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Centralising hyperacute stroke services in England: feasibility and compromises

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics

This study used aggregate patient counts only, obtained from HES. No individual patient-level data was sought, obtained or used in the study. No ethical approval was sought.

Authorship & contributorship

Michael Allen is the lead author and guarantor, and proposed the key methodology to be used in the study. He also contributed to coding of the model.

Kerry Pearn wrote much of the code used in the model, and contributed to refining the basis of the modelling. She was involved in reviewing and editing the paper.

Emma Villeneuve developed the initial prototypes of the model employed, testing a number of heuristic approaches. She was involved in reviewing and editing the paper.

Thomas Monks framed the initial problem of balancing access to stroke care with developing a unit of sufficient size to maintain expertise, and recommended the modelling study contained herein[1]. He critiqued the methods used in this study, and was involved in reviewing and editing the paper.

Ken Stein oversaw all work. He was involved in framing the problem to be modelled[1]. He critiqued the methods used in this study, and was involved in reviewing and editing the paper.

Martin James is the clinical stroke consultant for the work and paper. He was involved in framing the problem to be modelled[1]. He advised on the clinical objectives of the study. was involved in authoring, reviewing and editing the paper.

1. Monks T, Pitt M, Stein K, et al. Hyperacute stroke care and NHS England's business plan. BMJ 2014;34

Transparancy

The lead author (Michael Allen) confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

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Data sharing

Full data and code used for this study is available at:
https://github.com/MichaelAllen1966/stroke_unit_location

Included in the data and code are:
Counts of acute stroke admissions by LSOA
Estimated travel times from all LSOAs to al acute stroke units
Hospital information (name, location)
Full source code used to produce results reported here (which runs using open source software)

Abstract

Objectives: The policy of centralising hyperacute stroke units (HASUs) in England aims to provide stroke care in units that are both large enough to sustain expertise (>600 admissions/year) and dispersed enough to rapidly deliver time-critical treatments (<30 minutes maximum travel time). Currently, just over half (56%) of stroke patients access care in such a unit. We sought to model national configurations of HASUs that would optimise both institutional size and geographical access to stroke care, to maximise the population benefit from the centralisation of stroke care.

Design: Modelling of the effect of the national reconfiguration of stroke services. Optimal solutions were identified using a heuristic genetic algorithm.

Setting: 127 acute stroke services in England, serving a population of 54 million people.

Participants: 238,887 emergency admissions with acute stroke over a 3-year period (2013-2015).

Intervention: Modelled reconfigurations of HASUs optimised for institutional size and geographical access.

Main Outcome Measure: Travel distances and times to HASUs, proportion of patients attending a HASU with at least 600 admissions per year, minimum and maximum HASU admissions.

Results: Solutions were identified with 75-85 HASUs with annual stroke admissions in the range 600-2,000, which achieve up to 82% of patients attending a stroke unit within 30 minutes estimated travel time (with at least 95% and 98% patients being within 45 and 60 minutes travel time respectively).

Conclusions: The reconfiguration of hyperacute stroke services in England could lead to all patients being treated in a HASU with between 600 and 2,000 admissions per year. However, the proportion of patients within 30 minutes of a HASU would fall from over 90% to 80-82%.

Article summary

Strengths and weaknesses

- The study described allows for a national view of the relationship between the number of acute stroke units (based on choosing from current locations of acute stroke units) in England and the dual goals of (1) having all patients attend a stroke unit with at least 600 acute confirmed stroke admissions per year, and (2) having patients within 30 minutes of an acute stroke unit.
- The study uses a genetic algorithm that is able to hunt for solutions when there are a vast range of possibilities.
- The study takes an objective approach with explicitly described objectives.
- A limitation of the study is that identified solutions do not take into account the complex local pressures and reasons for preferring one unit over another at the cost of the objectives used in identifying solutions in this study.

Introduction

Stroke is a leading causes of death and disability worldwide, with an estimated 5.9 million deaths and 33 million stroke survivors in 2010[1]. In England, Wales and Northern Ireland 85,000 people are hospitalised with stroke each year[2], and stroke is ranked third as a cause of disability-adjusted life years in the UK over the last 25 years[3].

In recent years the NHS in England has sought to promote the reconfiguration of stroke services across the country, building on the evidence-based model developed in London[4]. Centralisation of stroke care in London has been shown to increase thrombolysis rates, reduce mortality, reduce length of stay, and reduce long-term costs to the NHS[5,6]. These benefits are considered to be due to patients being cared for by specialist stroke teams, facilitated by direct hospital admission to a large hyperacute stroke unit (HASU). Guidelines recommend a minimum number of admissions to a HASU of 600 patients per year, and NHS England reconfiguration guidelines also suggest 'travel time should be ideally 30 minutes but no more than 60 minutes[7,8]. Centralisation of acute stroke care in London was guided by a modelling exercise whereby sites were identified with no Londoner more than a 30 minute ambulance journey from the nearest HASU[5]. Time from onset to emergency hospital treatment is known to be especially critical for ischaemic stroke, when the effectiveness of thrombolysis declines rapidly in the first few hours after stroke[9]. More recently, mechanical thrombectomy has shown effectiveness in patients presenting up to 6 hours after stroke onset, with effectiveness still higher if treatment is given earlier[10].

With the critical importance of speed to treatment with thrombolysis or thrombectomy, it has nonetheless been questioned if the improvements in outcome that came with centralisation of stroke services in metropolitan areas could be replicated in more rural environments, with modelling being suggested as a first step at analysing the problem[11]. We therefore sought to investigate the potential for meeting the dual objectives of all patients with acute stroke being admitted to a HASU of sufficient size (at least 600 acute stroke patients per year) and that unit being within 30 minutes travel time.

Methods

We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England. No individual patient level data was accessed: counts of admissions per LSOA were extracted from Hospital Episode Statistics (HES; http://www.hscic.gov.uk/hes) using the Lightfoot Signals from Noise tool (http://www.lightfootsolutions.com/). Estimated fastest road travel times were obtained from a geographic information system (Maptitude, with MP-MileCharter add-in).

We used a genetic algorithm based on NSGA-II[12] (see online appendix) to derive potential configurations of HASUs across England, balancing competing objectives. Solutions were eliminated if another solution was equally as good in all optimisation parameters and was better in at least one parameter. The selected configurations were based on a range of optimisation parameters (listed in the online appendix) which seek to minimise travel distances and to control admission numbers (admitting as many people to HASUs with at least 600 admissions per year while also seeking to control the maximum number of admissions to any hospital). Solutions retained are referred to as non-dominated solutions; together these form a 'Pareto front' where improved performance in one objective can only be at the expense of another.

Results

When comparing predicted with actual admissions across the modlled configurations there was a median absolute error of 105 admissions per unit per year, or a relative absolute error of 17%. Prediction accuracy depended on proximity to a hospital's nearest neighbour, and was proportionately greater in urban areas where travel distance is less of a consideration. HASUs located close to other acutely admitting units have a poorer prediction accuracy than those located further from the nearest alternative acute stroke unit (figure 1).

With an increasing number of HASUs, average and maximum road travel times reduce (figure 2), following the law of 'diminishing returns'. For example, with 24 units (the number of neurosciences centres in England) the lowest average travel time is 34 minutes. As the number of HASUs is increased to 50, 75 and 100, the best average travel times found are 26, 22 and 19 minutes respectively. The best maximum travel time found are 109, 99, 78 and 78 minutes with 25, 50, 75 and 100 HASUs. Average and maximum travel times for the identified solutions depend on what other factors are prioritised in the model. For example, with 25 HASUs, average travel distances in different configurations (all of which are non-dominated solutions) range from 34 to 62 minutes, and maximum travel time range from 109 to 378 minutes.

As the number of HASUs increases, both the maximum and minimum number of admissions to any single hospital in the configuration reduces (figure 3). For example, with 25 units the lowest possible maximum number of admissions to any single unit is 4,381 admissions per year. With 50, 75 and 100 units the largest hospital has admissions of 2,493, 1,829 and 1,687 patients per year. These results represent the best compromise between unit size and distance if no other factors are regarded as important. To achieve all admissions attending a HASU with at least 600 admissions per year the maximum number of hospitals is 85, by which point 82% of the population is within 30 minutes travel (with 95% and 98% being within 45 and 60 minutes, and the maximum travel time is 99 minutes).

As the number of HASUs increases, the proportion of patients within 30 minutes travel increases (figure 4), to a maximum of 90% (the best possible proportions with 25, 50, 75 and 100 units were 52%, 70%, 84% and 88%). At the same time, increasing the number of HASUs reduces the number of patients attending a unit with at least 600 admissions per year (figure 4). Increasing the number of units lead first to an increase in the proportion of patients attending a unit of sufficient size within 30 minutes travel, but when increased further a reduction in this proportion is seen (figure 4). The maximum proportion of patients attending a unit admitting 600 patients per year within 30 minutes travel is 82%. Solutions with at least 80% of patients being within 30 minutes of a HASU admitting at least 600 patients per year have between 75 and 95 HASUs. If target maximum travel time is extended to 45 minutes then the maximum proportion of patients attending a HASU of sufficient size is 95%, with this maximum occurring with between 65 and 90 units.

In each configuration it may be important to control the maximum number of admissions to any single unit. Configurations of between 75 and 85 HASUs were identified with all patients attending a unit admitting 600 patients per year, at least 80% of patients within 30 minutes travel and maximum admissions to any single HASU of no greater than 2,000. The algorithm identified 140 configurations in which annual admissions were kept within 600-2,500, at least 80% of patients were within 30 minutes of their closest HASU, and at least 95% and 98% of patients were with 45 and 60 minutes of their closest unit.

Discussion

Our modelling of national configurations of HASUs, designed to replicate the population benefits from centralisation of acute stroke services, has shown the feasibility but also the compromises necessary to maximise these benefits. Currently just over half (56%) of patients with acute stroke are admitted to a stroke unit with at least 600 admissions per year[2], and NHS England proposes to increase this proportion through centralisation in fewer, larger units[13]. By reducing from the current 127 sites to between 75-85 centres, our centralised HASU model predicts it is possible for all stroke patients to attend a unit of sufficient size, but with a reduction in the proportion of patients within 30 minutes travel from the current 90% to 80-82%, and with 97% and 99% of patients within 45 and 60 minutes travel respectively.

Maximising the number of patients attending a HASU with 600 stroke admissions per year is not an end in itself. The figure is an approximation for the size of a HASU able to develop and sustain expertise in stroke care[8], and overcome identified barriers to improved care such as thrombolysis[14–16]. An association has been observed between door-to-needle time for thrombolysis and institutional size[17,18]. Patients admitted to HASUs in areas that have undergone centralisation were found to be more likely to receive other important clinical interventions such as brain scanning and direct admission to a stroke unit sooner[19]. Centralisation to 75-85 hospitals in the manner we have described could therefore be expected to provide a significant benefit to the majority of patients. To yield these benefits, the large majority of patients will travel only moderately further (if at all) to reach a HASU. The disbenefits are to approximately 2% of the population who would be more than 60 minutes away from a reconfigured HASU, and to the 2% of patients who are currently within 30 minutes of an existing centre but who, with centralisation, will travel more than 45 minutes to their nearest HASU. Consideration is therefore needed of how the disbenefits for these patients might be mitigated. Increased travel times might offset by targeted stroke awareness campaigns (which have been shown to enhance patient response to suspected stroke[20]) leading to earlier contact of emergency services. Increased travel time may also be offset by reduced door-to-treatment time in the HASU[17,21]. More radical solutions for isolated areas include mobile diagnosis and treatment [22]. Early diagnostic access and intravenous thrombolysis is a particular issue given the paucity of geographical coverage of mechanical thrombectomy in the UK, which promotes a model of ‘drip-and-ship’ (near-patient thrombolysis followed by immediate transfer to a more distant thrombectomy centre); currently only 75% of the English population is within 45 minutes travel time of one of the current 24 neurosciences centres, where the expertise in this procedure is exclusively concentrated. All of these impacts from reconfiguration are not uniformly distributed, but fall disproportionately on more rural populations, and the existing evidence base from predominantly metropolitan reconfigurations[5,23] does not allow a precise estimate of the trade-offs at hand when balancing locality against institutional size – a limitation that will hamper professional and public debate regarding the benefits and consequences of large service reorganisations.

In constructing our model, we have assumed all patients will be taken to their closest HASU. If this is not the case (such as decisions being made instead on organisational boundaries) then some inaccuracy of the model around those boundaries is expected. This will be especially true in areas that have more than one HASU in close proximity; in such cases choice of destination may be influenced by factors (such as institutional reputation) other than shortest travel time. With increasing centralisation inaccuracies due to the proximity of units will reduce, as fewer patients will be on the boundary where travel time is not the only influence on the destination. Though we have incorporated the size of HASU into the algorithm, we have also sought to avoid infeasibly large units (those with more than 2,500 stroke admissions/year), particularly as such an arrangement involves large numbers of stroke-like presentations ('stroke mimics') also being conveyed to a HASU – such mimics represent as much as an additional 32% of admissions[24]. Centralisation therefore raises significant issues around the capacity of receiving HASUs, both in infrastructure and workforce. Continued capacity at any HASU will depend on the efficient repatriation to locally-based post-acute and rehabilitation services (e.g. after the first 48-72 hours of care), and we have not modelled these effects or their vulnerability in this paper. There is also uncertainty around the recommended target of 600 admissions per year, not least as random variation would be expected to vary this figure between 550-650 (based on a Poisson distribution). With an ageing population, however, we anticipate a steady increase in admissions to hospital with disabling stroke despite better preventative care, particularly in stroke related to atrial fibrillation[25]

Care should always be taken when considering what appear to be mathematically 'optimal' solutions. A model of this size identifies many solutions that have very similar performance, with only marginal differences between them. Our results are therefore best interpreted as showing the broad number of HASUs that are needed on a national or regional scale to deliver the maximum benefit from centralisation, and what impact this is likely to have on a significant minority of patients. Multiple objective optimisation location problems rarely if ever have a single explicit solution, and can illuminate but not dictate regional planning which is still best conducted on a smaller scale, incorporating other local knowledge. Nonetheless, national-level analysis can provide an insight into the range of optimal distributions of stroke centres across England. The national algorithm has identified many possible configurations in which annual admissions to any HASU are within the range 600-2,500 and with at least 80% of patients within 30 minutes of their closest HASU. Choosing between approximately similar options will require other considerations to be taken into account, and this is best performed at a regional level – although not at the relatively small 'footprint' of many of NHS England's 44 Sustainability and Transformation Plans (STPs), the current geographical unit of planning.

Acute stroke care is evolving, and the development of mechanical thrombectomy for acute large artery stroke is likely to create an imperative for still greater centralisation of services[10]. The geographical issues we have identified here will act as an even greater influence on service planning for such specialised treatment, with a similar or more pronounced differential effect between urban and rural environments – removing, for example, the rationale for any metropolitan HASU that is not also capable of delivering mechanical thrombectomy. Further modelling work should be focussed on how best to organise care across England when still greater centralisation of some services are required for a significant proportion of patients.

Conclusions

A policy of centralising acute stroke services across England in 75-85 HASUs could realistically achieve 80-85% of patients attending an acute unit of sufficient size within 30 minutes travel time (with 97% and 99% being within 45 and 60 minutes travel respectively), and with no unit larger than 2,500 stroke admissions per year. Though centralisation could offer significant advantages to the large majority of patients, a small minority (2-4% of the population) would be significantly adversely affected by centralisation, and planning for this minority will inevitably involve compromise between the recommended ideal institutional size and travel times.

What is known already, and what this study adds

What is known already?

NHS England's policy for the centralisation of acute stroke care is based on observational evidence of the mortality benefits from such centralised services, and recommends that all patients should attend a hyperacute stroke unit that both admits at least 600 acute stroke patients per year and is within 30 minutes travel time. Currently just over half (55%) of patients in England receive care at a HASU fulfilling both these conditions.

What this study adds

Applying a multi-objective genetic algorithm approach, we predict that centralising acute stroke services across England in 75-85 HASUs (from the present 127 stroke centres) could realistically achieve all patients attending a stroke unit which has at least 600 acute stroke admissions per year, with 82%, 97% and 99% patients being within 30, 45 and 60 minutes travel respectively. The disbenefit to a significant rural minority is that approximately 7% of patients will move out of a 30 minute travel distance, and an additional 0.7% of patients move out of a 60 minute travel distance.

Acknowledgements

This study was funded by the National Institute of Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care for the South West Peninsula. The views and opinions expressed in this paper are those of the authors, and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

References

1 Feigin VL, Forouzanfar MH, Krishnamurthi R, *et al.* Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *Lancet* 2014;**383**:245–55. doi:10.1016/S0140-6736(13)61953-4

2 Sentinel Stroke Audit Programme (SSNAP). Apr2015Mar2016-AnnualResultsPortfolio. Natl. Results April 2015-Mar 2016 https//www.strokeaudit.org/Documents/Results/National/Apr2015Mar2016/Apr2015Mar2016-AnnualResultsPortfolio.aspx. 2016.

3 Newton JN, Briggs ADM, Murray CJL, *et al.* Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;**386**:2257–74. doi:10.1016/S0140-6736(15)00195-6

4 NHS England. Putting Patients First. NHS England's business plan 2014/15–2016/17. *https://www.england.nhs.uk/wp-content/uploads/2014/04/ppf-1415-1617-wa.pdf* 2014.

5 Morris S, Hunter RM, Ramsay AIG, *et al.* Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *BMJ* 2014;**349**:g4757. doi:10.1136/bmj.g4757

6 Hunter RM, Davie C, Rudd A, *et al.* Impact on Clinical and Cost Outcomes of a Centralized Approach to Acute Stroke Care in London: A Comparative Effectiveness Before and After Model. *PLoS One* 2013;**8**:1–9. doi:10.1371/journal.pone.0070420

7 Price C, James M. Meeting the Future Challenge of Stroke Meeting the Future Challenge of Stroke. Br. Assoc. Stroke Physicians. 2011.www.basp.ac.uk

8 NHS England. Stroke Services: Configuration Decision Support Guide (www.eoescn.nhs.uk/index.php/download_file/force/2069/168/). 2015.

9 Emberson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet* 2014;**384**:1929–35. doi:10.1016/S0140-6736(14)60584-5

10 Goyal M, Menon BK, Van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;**387**:1723–31. doi:10.1016/S0140-6736(16)00163-X

11 Monks T, Pitt M, Stein K, *et al.* Hyperacute stroke care and NHS England's business plan. *BMJ* 2014;**348**:g3049. doi:10.1136/bmj.g3049

12 Deb K, Pratap A, Agarwal S, *et al.* A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans Evol Comput* 2002;**6**:182–97. doi:10.1109/4235.996017

13 NHS England. NHS England Business Plan 2016/17. 2016.https://www.england.nhs.uk/wp-content/uploads/2016/03/bus-plan-16.pdf

14 Eissa A, Krass I, Bajorek B V. Barriers to the utilization of thrombolysis for acute ischaemic stroke. *J Clin Pharm Ther* 2012;**37**:399–409. doi:http://dx.doi.org/10.1111/j.1365-2710.2011.01329.x

15 Carter-Jones CR. Stroke thrombolysis: Barriers to implementation. Int. Emerg. Nurs. 2011;**19**:53–7. doi:10.1016/j.ienj.2010.02.005

16 Monks T, Pitt M, Stein K, *et al.* Maximizing the population benefit from thrombolysis in acute ischemic stroke: A modeling study of in-hospital delays. *Stroke* 2012;**43**:2706–11. doi:10.1161/STROKEAHA.112.663187

17 Bray BD, Campbell J, Cloud GC, *et al.* Bigger, faster?: Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke* 2013;**44**:3129–35. doi:10.1161/STROKEAHA.113.001981

18 Strbian D, Ahmed N, Wahlgren N, *et al.* Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry. *Stroke* 2015;**46**:1275–80. doi:10.1161/STROKEAHA.114.007170

19 Ramsay AIG, Morris S, Hoffman A, *et al.* Effects of centralizing acute stroke services on stroke care provision in two large metropolitan areas in England. *Stroke* 2015;**46**:2244–51. doi:10.1161/STROKEAHA.115.009723

20 Mellon L, Doyle F, Rohde D, *et al.* Stroke warning campaigns: delivering better patient outcomes? A systematic review. *Patient Relat Outcome Meas* 2015;**6**:61–73. doi:10.2147/PROM.S54087

21 Meretoja A, Strbian D, Mustanoja S, *et al.* Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology* 2012;**79**:306–13. doi:10.1212/WNL.0b013e31825d6011

22 Kunz A, Ebinger M, Geisler F, *et al.* Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol* 2016;**15**:1035–43. doi:10.1016/S1474-4422(16)30129-6

23 Fulop N, Boaden R, Hunter R, *et al.* Innovations in major system reconfiguration in England: a study of the effectiveness, acceptability and processes of implementation of two models of stroke care. *Implement Sci* 2013;**8**:5. doi:10.1186/1748-5908-8-5

24 Dawson A, Cloud GC, Pereira AC, *et al.* Stroke mimic diagnoses presenting to a hyperacute Stroke unit. *Clin Med J R Coll Physicians London* 2016;**16**:423–6. doi:10.7861/clinmedicine.16-5-423

25 Yiin GSC, Howard DPJ, Paul NLM, *et al.* Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular

events: a population-based study. *J Neurol Neurosurg Psychiatry* 2015;:1–7. doi:10.1136/jnnp-2015-311947

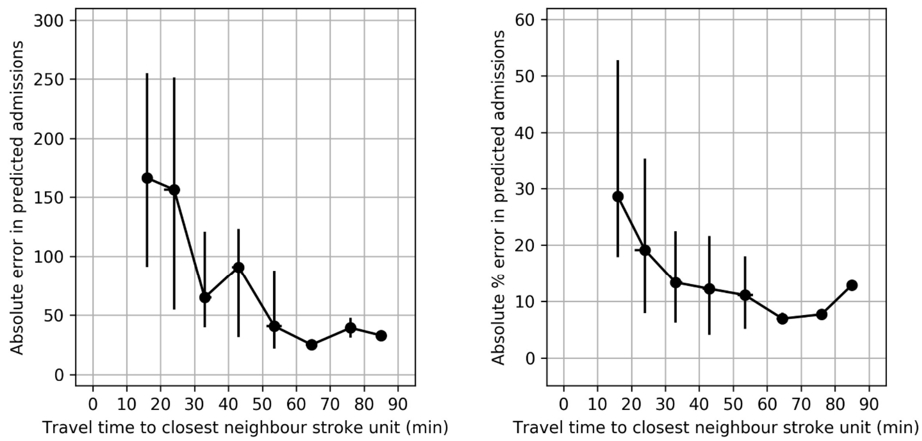
Figure legends

Figure 1. Error in predicting admissions (as recorded in SSNAP) grouped by proximity to the closest neighbouring acute stroke unit (10 minute bins). Points show median with error bars indicating inter-quartile range. The left panel shows the absolute error in predicting admission numbers per year, the right panel shows the absolute error as a percentage of actual admissions for each unit.

Figure 2. The effect of changing the number of acute stroke units on average and maximum travel times. The left panel shows the best average and maximum travel times achieved by the algorithm. The middle panel shows average travel times. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average travel time and other optimisation parameters. The right panel repeats these results for maximum travel time.

Figure 3 The effect of changing the number of acute stroke units on minimum and maximum admissions to any single unit. The left panel shows the best admissions identified by the algorithm (it is better to have a higher minimum number of admissions and lower maximum admissions; that is the smallest hospital should be as large as possible, and the largest hospital as small as possible). The middle panel shows minimum admission numbers (to the smallest unit in each scenario). The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average minimum admissions and other optimisation parameters. The right panel repeats these results for maximum admissions in a scenario.

Figure 4 The effect of changing the number of acute stroke units on the proportion of patients attending a unit with 600 admissions per year, the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location. The top left panel shows the best solutions for each identified by the algorithms. The top right panels shows the proportion of patients attending a unit with 600 admissions per year. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between attending a unit with target admission numbers and other optimisation parameters. The bottom two panels repeat the analysis for the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location.



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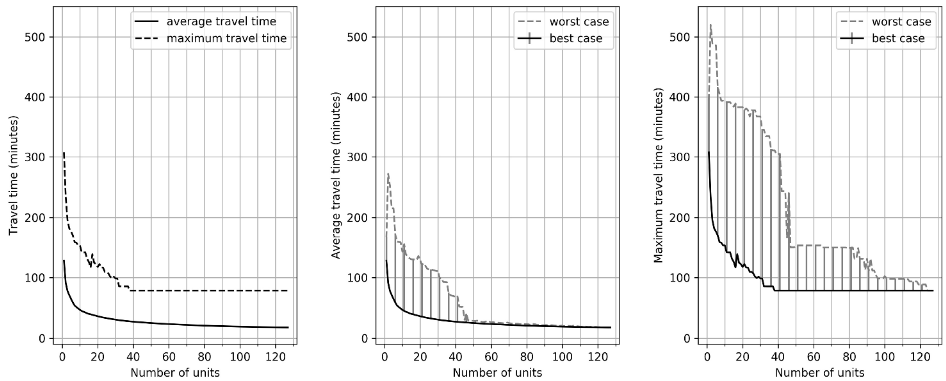

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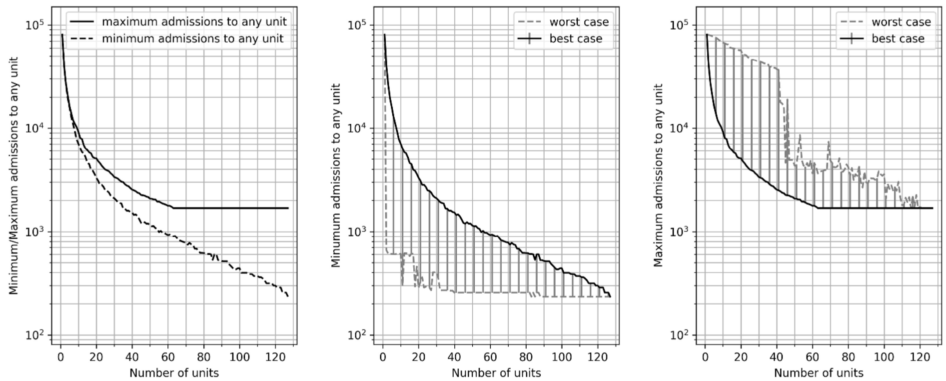

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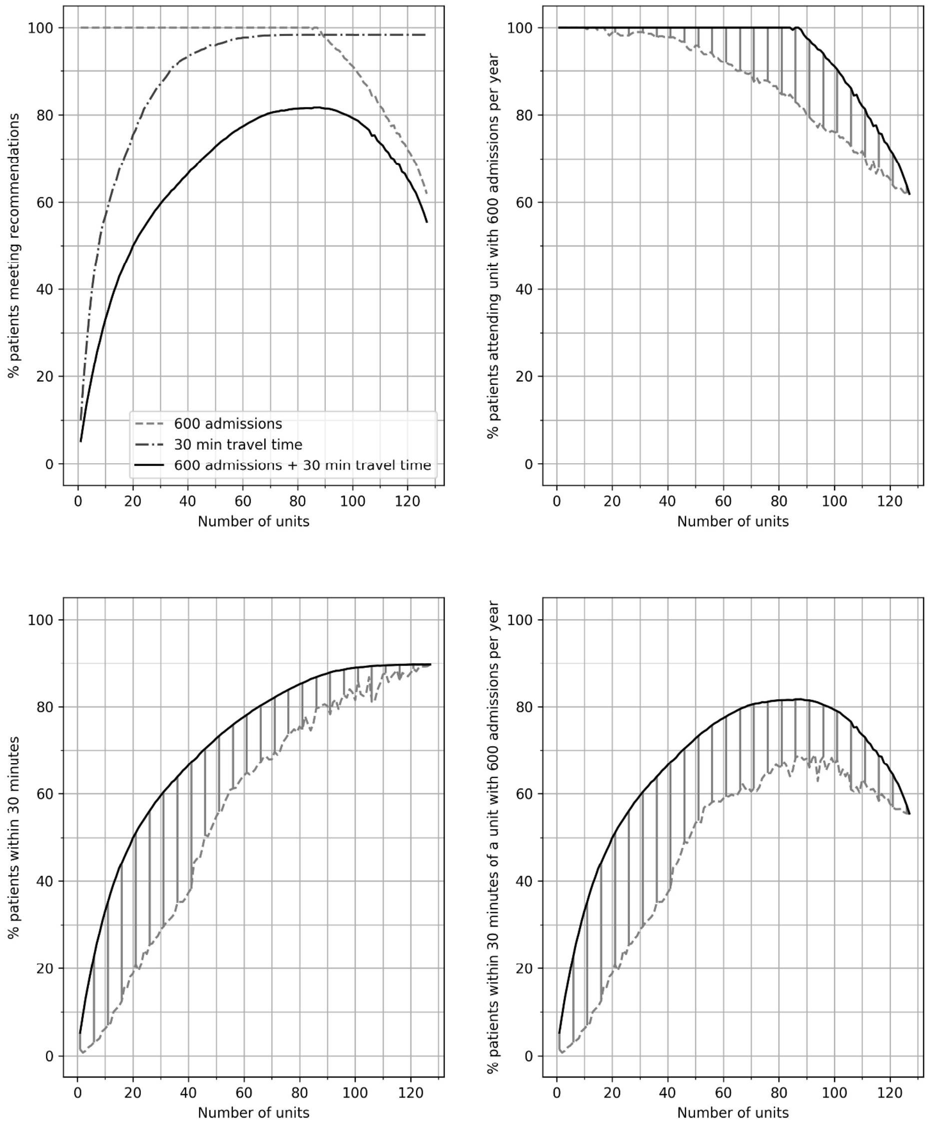

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Appendix

1. Code and data repository

Data and code used for the model are available at:
https://github.com/MichaelAllen1966/stroke_unit_location

2. NSGA-II overview

The Genetic Algorithm used for this study was based on NSGA-II[1]. This method evolves solutions based on multiple objectives, but without any weighting of objectives. In each generation, the Pareto front of non-dominated solutions is identified. A solution is non-dominated if there are no other solutions at least equal in all objectives and better in at least one objective. Larger populations may be selected by picking subsequent Pareto fronts (re-evaluation the Pareto front after removal of the previous Pareto front identified).

An example of a Pareto front using two objectives is shown in figure 1.

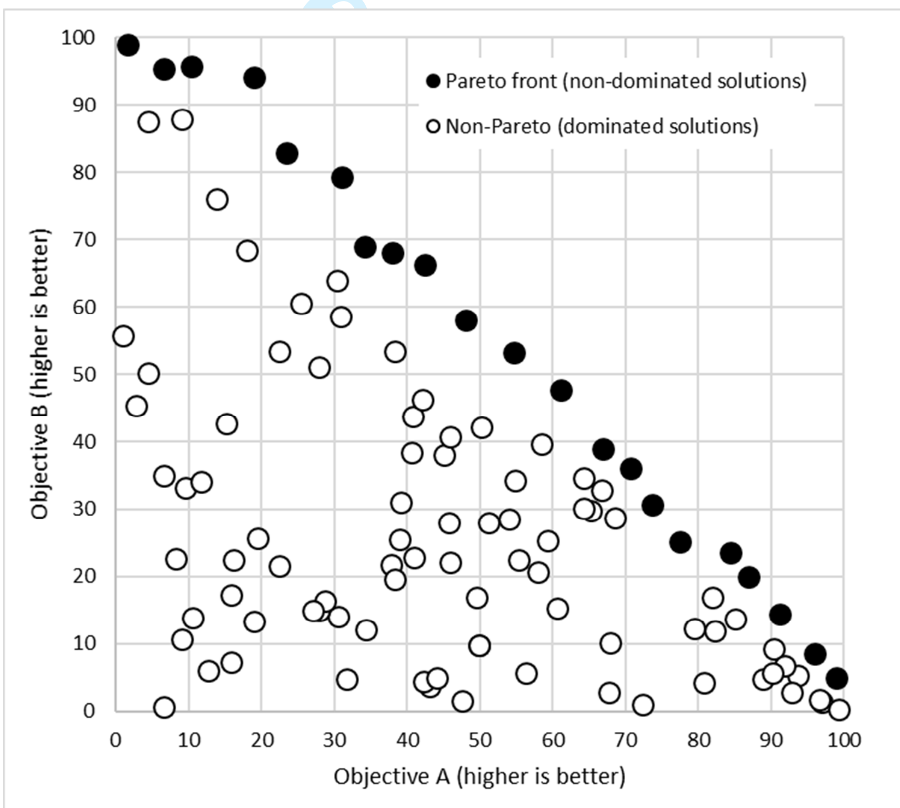

Figure 1. Example of identification of Pareto front (non-dominated) points when comparing two objectives.

2.1. Algorithm objectives

The objectives which could be used for genetic selection were:

1: Number of hospitals (lower is better)

2: Average travel time (lower is better)

3: Maximum travel time (lower is better)

4: Maximum admissions to any one hospital (lower is better)

5: Minimum admissions to any one hospital (higher is better)

6: Max/Min admissions ratio (lower is better)

7: Proportion patients within estimated 30 min travel distance (higher is better)

8: Proportion patients within estimated 45 min travel distance time (higher is better)

9: Proportion patients within estimated 60 min travel distance time (higher is better)

10: Proportion patients attending unit with target admission numbers (higher is better)

11: Proportion patients attending unit with target admission numbers and within estimated 30 min travel time (higher is better)

12: Proportion patients attending unit with target admission numbers and within estimated 45 min travel time (higher is better)

13: Proportion patients attending unit with target admission numbers and within estimated 60 min travel time (higher is better)

Attempting to optimise on all 13 objectives simultaneously produces slow progress. In order to produce the final solution set a number of runs with more restricted objectives were performed. These were then used as a seed population for further breeding which were then selected based on all objectives.

2.2. Description of the genetic algorithm

1) Code 127 hospitals (SSNAP acute admitting stroke units) as open/closed binary string of genes.

    i) e.g. 001011 would be six genes that represent hospitals 3,5&6 being open and 1,2,&4 being closed

2) Identify which combination of objectives to use for selection in algorithm (may be from 2 objectives to all objectives).

3) Set up initial population of solutions (a typical starting population is 10,000 solutions).

    i) Randomly choose number of hospitals to open in each solution.

    ii) Randomly assign open hospitals.

    iii) A library of solutions may be imported instead of, or in addition to, a random population of solutions.

    iv) Non-unique solutions are removed.

4) Breed solutions.

   i) Choose pairs of solutions at random from the population.

   ii) Select a single crossover point is at random within the solution binary string.

   iii) Join the left section (before the crossover point) of one parent solution to the right section (from the crossover-point rightwards) of the second parent solution to form a new 'child' solution. Produce a second child solution by combining the remaining sections of each parent solution.

   e.g. a crossover at point five would perform the following:

   Parent A: 1 1 1 1 1 1

   Parent B: 0 0 0 0 0 0

   Child A: 1 1 1 1 0 0

   Child B: 0 0 0 0 1 1

   iv) Perform breeding so that there are as many children as parents.

   v) Randomly mutate children: there is a given probability that any binary element will switch to the opposite (a random mutation probability per element of 0.002 was typically used).

   vi) Combine parents and children to for a new population.

   vii) Remove non-unique solutions and any solutions where all hospitals are closed.

5) Calculate the performance of all solutions against the objectives used for selection

6) Identify all non-dominated (Pareto front) solutions

   i) If the number of selected solutions is greater than the maximum permitted breeding population then reduce the number f solutions by either 1) picking solutions at random to obtain the required number of solutions to pass on to the next generation, or (2) pick two solutions and randon and use tournament selection based on crowding distance (a measure of how close the solution scores are to nearest neighbour scoring solutions)

   ii) If the number of selected solutions is lower than the minimum permitted breeding population then remove the previously selected non-dominated solutions and repeat the Pareto selection until sufficient solutions have been identified (if a selection produces more than the maximum number of selected solutions, then random selection is performed just on the last Pareto front in order not to exceed the maximum number of solutions to pass on to the next generation.

   iii) Store the first Pareto front solutions.

   iv) Note: The minimum and maximum number of solutions to pass on to the next generation may be the same number to keep solution size constant. Alternatively, a range of population size may be acceptable (e.g. a minimum number of 1,000 solutions may be chosen, but a maximum number of 5,000 solutions may be permitted. In this case Pareto selection is repeated until at least 1,000 solutions have been selected, but restriction on the number of solutions only occurs if the number of solutions chosen exceeds 5,000).

7) Repeat steps 4-6 until the maximum number of generations is reached or the algorithm is stopped by another indicator.

   i) Population diversity is monitored using average Hamming distance. The Hamming distance between any two solutions is the proportion of genes that are different. Average Hamming distance is the mean Hamming distances for all pairwise comparisons in the population (after first Pareto front selection). Genetic algorithms were typically stopped when there was a change of <0.001 in average Hamming distance across 5 generations.

References

1. Deb, K., Pratap, A., Agarwal, S. & Meyarivan, T. A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans. Evol. Comput.* **6,** 182–197 (2002).

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Feasibility of a hyper-acute stroke unit model of care across England. A modelling analysis.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics

This study used aggregate patient counts only, obtained from HES. No individual patient-level data was sought, obtained or used in the study. No ethical approval was sought.

Authorship & contributorship

Michael Allen is the lead author and guarantor, and proposed the key methodology to be used in the study. He also contributed to coding of the model.

Kerry Pearn wrote much of the code used in the model, and contributed to refining the basis of the modelling. She was involved in reviewing and editing the paper.

Emma Villeneuve developed the initial prototypes of the model employed, testing a number of heuristic approaches. She was involved in reviewing and editing the paper.

Thomas Monks framed the initial problem of balancing access to stroke care with developing a unit of sufficient size to maintain expertise, and recommended the modelling study contained herein[1]. He critiqued the methods used in this study, and was involved in reviewing and editing the paper.

Ken Stein oversaw all work. He was involved in framing the problem to be modelled[1]. He critiqued the methods used in this study, and was involved in reviewing and editing the paper.

Martin James is the clinical stroke consultant for the work and paper. He was involved in framing the problem to be modelled[1]. He advised on the clinical objectives of the study, was involved in authoring, reviewing and editing the paper.

1. Monks T, Pitt M, Stein K, et al. Hyperacute stroke care and NHS England's business plan. BMJ 2014;34

Transparancy

The lead author (Michael Allen) confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

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Data sharing

Full data and code used for this study is available at:
https://github.com/MichaelAllen1966/stroke_unit_location

Included in the data and code are:
Counts of acute stroke admissions by LSOA
Estimated travel times from all LSOAs to all acute stroke units
Hospital information (name, location)
Full source code used to produce results reported here (which runs using open source software)

Abstract

Objectives: The policy of centralising hyperacute stroke units (HASUs) in England aims to provide stroke care in units that are both large enough to sustain expertise (>600 admissions/year) and dispersed enough to rapidly deliver time-critical treatments (<30 minutes maximum travel time). Currently, just over half (56%) of stroke patients access care in such a unit. We sought to model national configurations of HASUs that would optimise both institutional size and geographical access to stroke care, to maximise the population benefit from the centralisation of stroke care.

Design: Modelling of the effect of the national reconfiguration of stroke services. Optimal solutions were identified using a heuristic genetic algorithm.

Setting: 127 acute stroke services in England, serving a population of 54 million people.

Participants: 238,887 emergency admissions with acute stroke over a 3-year period (2013-2015).

Intervention: Modelled reconfigurations of HASUs optimised for institutional size and geographical access.

Main Outcome Measure: Travel distances and times to HASUs, proportion of patients attending a HASU with at least 600 admissions per year, minimum and maximum HASU admissions.

Results: Solutions were identified with 75-85 HASUs with annual stroke admissions in the range 600-2,000, which achieve up to 82% of patients attending a stroke unit within 30 minutes estimated travel time (with at least 95% and 98% patients being within 45 and 60 minutes travel time respectively).

Conclusions: The reconfiguration of hyperacute stroke services in England could lead to all patients being treated in a HASU with between 600 and 2,000 admissions per year. However, the proportion of patients within 30 minutes of a HASU would fall from over 90% to 80-82%.

Article summary

Strengths and weaknesses

- The study described allows for a national view of the relationship between the number of acute stroke units (based on choosing from current locations of acute stroke units) in England and the dual goals of (1) having all patients attend a stroke unit with at least 600 acute confirmed stroke admissions per year, and (2) having patients within 30 minutes of an acute stroke unit.
- The study uses a genetic algorithm that is able to hunt for solutions when there are a vast range of possibilities.
- The study takes an objective approach with explicitly described objectives.
- A limitation of the study is that identified solutions do not take into account the complex local pressures and reasons for preferring one unit over another at the cost of the objectives used in identifying solutions in this study.

Introduction

Stroke is a leading cause of death and disability worldwide, with an estimated 5.9 million deaths and 33 million stroke survivors in 2010[1]. In England, Wales and Northern Ireland 85,000 people are hospitalised with stroke each year[2], and stroke is ranked third as a cause of loss of disability-adjusted life years in the UK over the last 25 years[3].

In recent years the NHS in England has sought to promote the reconfiguration of stroke services across the country, building on the evidence-based model developed in London[4]. Centralisation of stroke care in London has been shown to increase thrombolysis rates, reduce mortality, reduce length of stay, and reduce long-term costs to the NHS[5,6]. These benefits are considered to be due to patients being cared for by specialist stroke teams, facilitated by direct hospital admission to a large hyperacute stroke unit (HASU). In the HASU model of care patients are taken directly to units which may provide immediate response to stroke, including assessment, stabilisation and any primary intervention, before later discharge or transfer to step-down local stroke units[7]. Guidelines recommend a minimum number of admissions to a HASU of 600 patients per year, and NHS England reconfiguration guidelines also suggest ‘travel time should be ideally 30 minutes but no more than 60 minutes’[8,9]. Centralisation of acute stroke care in London was guided by a modelling exercise whereby sites were identified with no Londoner more than a 30 minute ambulance journey from the nearest HASU[5]. Time from onset to emergency hospital treatment is known to be especially critical for ischaemic stroke, when the effectiveness of thrombolysis declines rapidly in the first few hours after stroke[10]. More recently, mechanical thrombectomy has shown effectiveness in patients presenting up to 6 hours after stroke onset, with effectiveness still higher if treatment is given earlier[11].

With the critical importance of speed to treatment with thrombolysis or thrombectomy, it has nonetheless been questioned if the improvements in outcome that came with centralisation of stroke services in metropolitan areas could be replicated in more rural environments, with modelling being suggested as a first step at analysing the problem[12]. We therefore sought to investigate the potential for meeting the dual objectives of all patients with acute stroke being admitted to a HASU of sufficient size (at least 600 acute stroke patients per year) and that unit being within 30 minutes travel time. The modelling described here focusses on the Hyper Acute Stroke Unit phase of stroke care[7] and does not extend to organisation of ongoing step-down care in local stroke units, or after discharge home.

Methods

Detailed methods, with links to underlying data and source code used, are given in the on-line appendix.

The model predicts, for any configuration of HASUs, the travel times (fastest road travel time chosen, from home location of patient to hospital with the shortest estimated travel time), and the number of admissions to each HASU. A genetic algorithm was used to identify good configurations.

We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England. No individual patient level data was accessed: counts of admissions per LSOA were extracted from Hospital Episode Statistics (HES; http://www.hscic.gov.uk/hes) with access to national HES data managed through Lightfoot Solutions (http://www.lightfootsolutions.com/). Estimated fastest road travel times were obtained from a geographic information system (Maptitude, with MP-MileCharter add-in).

We used a genetic algorithm based on NSGA-II[13] to derive potential configurations of HASUs across England, balancing competing objectives. Solutions were eliminated if another solution was equally as good in all optimisation parameters and was better in at least one parameter. The selected configurations were based on a range of optimisation parameters (listed in the online appendix) which seek to minimise travel distances and to control admission numbers (admitting as many people to HASUs with at least 600 admissions per year while also seeking to control the maximum number of admissions to any hospital). Solutions retained are referred to as non-dominated solutions; together these form a 'Pareto front' where improved performance in one objective can only be at the expense of another.

Results

The model assumes patients attend the hospital closest to their home location. In order to test this assumption we compared admissions predicted assuming that the closest hospital was used with actual admissions to each hospital. When comparing predicted with actual admissions there was a median absolute error of 105 admissions per unit per year, or a relative absolute error of 17%. Prediction accuracy depended on proximity to a hospital's nearest neighbour, and was proportionately greater in urban areas where travel distance is less of a consideration. HASUs located close to other acutely admitting units have a poorer prediction accuracy than those located further from the nearest alternative acute stroke unit (figure 1). These results gave confidence in progressing with the basic model assumption that patients should generally attend their closest unit.

With an increasing number of HASUs, average and maximum road travel times reduce (figure 2), following the law of 'diminishing returns'. For example, with 24 units (the number of neuroscience centres in England) the lowest average travel time is 34 minutes. As the number of HASUs is increased to 50, 75 and 100, the best average travel times found are 26, 22 and 19 minutes respectively. The best maximum travel time found are 109, 99, 78 and 78 minutes with 25, 50, 75 and 100 HASUs. Average and maximum travel times for the identified solutions depend on what other factors are prioritised in the model. For example, with 25 HASUs, average travel distances in different configurations (all of which are non-dominated solutions) range from 34 to 62 minutes, and maximum travel time range from 109 to 378 minutes.

As the number of HASUs increases, both the maximum and minimum number of admissions to any single hospital in the configuration reduces (figure 3). For example, with 25 units the lowest possible maximum number of admissions to any single unit is 4,381 admissions per year. With 50, 75 and 100 units the largest hospital has admissions of 2,493, 1,829 and 1,687 patients per year. These results represent the best compromise between unit size and distance if no other factors are regarded as important. To achieve all admissions attending a HASU with at least 600 admissions per year the maximum number of hospitals is 85, by which point 82% of the population is within 30 minutes travel (with 95% and 98% being within 45 and 60 minutes, and the maximum travel time is 99 minutes).

As the number of HASUs increases, the proportion of patients within 30 minutes travel increases (figure 4), to a maximum of 90% (the best possible proportions with 25, 50, 75 and 100 units were 52%, 70%, 84% and 88%). At the same time, increasing the number of HASUs reduces the number of patients attending a unit with at least 600 admissions per year (figure 4). Increasing the number of units lead first to an increase in the proportion of patients attending a unit of sufficient size within 30 minutes travel, but when increased further a reduction in this proportion is seen (figure 4). The maximum proportion of patients attending a unit admitting 600 patients per year within 30 minutes travel is 82%. Solutions with at least 80% of patients being within 30 minutes of a HASU admitting at least 600 patients per year have between 75 and 95 HASUs. If target travel time is increased from 30 to 45 minutes then the maximum proportion of patients attending a HASU of sufficient size is 95%, with this maximum occurring with between 65 and 90 units.

In each configuration it may be important to control the maximum number of admissions to any single unit. Configurations of between 75 and 85 HASUs were identified with all patients attending a unit admitting 600 patients per year, at least 80% of patients within 30 minutes travel and maximum admissions to any single HASU of no greater than 2,000. The algorithm identified 93 configurations in which annual admissions were kept within 600-2,000, at least 80% of patients were within 30 minutes of their closest HASU, and at least 95% and 98% of patients were with 45 and 60 minutes of their closest unit. The distribution of size of unit, among all solutions with yearly admissions per unit within the 600 to 2,000 range was skewed significantly towards lower admissions (figure 5), with only 10% of units having more than 1,500 admissions per year.

Discussion

Our modelling of national configurations of HASUs, designed to replicate the population benefits from centralisation of acute stroke services, has shown the feasibility but also the compromises necessary to maximise these benefits. Currently just over half (56%) of patients with acute stroke are admitted to a stroke unit with at least 600 admissions per year[2], and NHS England proposes to increase this proportion through centralisation in fewer, larger units[14]. These HASUs would have staffing levels and competencies as specified in national standards[15,16], and provide intensive (level 2) nursing and medical care for the initial 72 hours after onset (on average) before repatriation of the patient once medically stable to local step-down services for ongoing acute care and rehabilitation. By reducing from the current 127 acute sites to between 75-85 HASUs, our centralised HASU model predicts it is possible for all stroke patients to attend a unit of sufficient size, but with a reduction in the proportion of patients within 30 minutes travel from the current 90% to 80-82%, and with 95% and 98% of patients within 45 and 60 minutes travel respectively.

Maximising the number of patients attending a HASU with at least 600 stroke admissions per year is not an end in itself. The figure is an approximation for the size of a HASU able to develop and sustain expertise in stroke care[9], and overcome identified barriers to improved care such as thrombolysis[17–19]. An association has been observed between door-to-needle time for thrombolysis and institutional size[20,21]. Patients admitted to HASUs in areas that have undergone centralisation were found to be more likely to receive other important clinical interventions such as brain scanning and direct admission to a stroke unit sooner[22]. However, the corollary of such centralisations is the creation of very large units: the most recent Greater Manchester reconfiguration has created one HASU with over 2,000 stroke admissions/year. Our modelling has explored the compromises between institutional size and distance, and the differential effects from centralisation in urban and rural areas. In seeking to balance these often competing priorities, we sought solutions where the largest unit had fweer than 2,000 confirmed stroke admissions per year. We observed that in centralised solutions with all hospital admissions between 600 and 2,000 admissions per year, fewer than 10% of hospitals would have admissions of more than 1,500 per year. Nevertheless, large-scale reconfigurations raise significant issues around the capacity of a small number of very large receiving HASUs, both in infrastructure and workforce, and the potential disbenefits of such large units (if any) are much less well understood. Centralisation to 75-85 hospitals in the manner we have described could therefore be expected to provide a significant benefit to the majority of patients. To yield these benefits, the large majority of patients will travel only moderately further (if at all) to reach a HASU. The disbenefits are to approximately 1.5% of the population who would be more than 60 minutes away from a reconfigured HASU (compared with an estimated 0.3% with all current acute stroke units), and to the 2% of patients who are currently within 30 minutes of an existing centre but who, with centralisation, will travel more than 45 minutes to their nearest HASU. Consideration is therefore needed of how the disbenefits for these patients might be mitigated. Increased travel times might be offset by targeted stroke awareness campaigns (which have been shown to enhance patient response to suspected stroke[23]) leading to earlier contact of emergency services. Increased travel time may also be offset by reduced door-to-treatment time in the HASU[20,24]. More radical solutions for isolated areas include mobile diagnosis and treatment[25]. Early diagnostic access and intravenous thrombolysis is a particular issue given the paucity of geographical coverage of mechanical thrombectomy in the UK, which promotes a model of ‘drip-and-ship’ (near-patient thrombolysis followed by immediate transfer to a more distant thrombectomy centre); currently only 75% of the English population is within 45 minutes travel time of one of the current 24 neurosciences centres, where the expertise in this procedure is exclusively concentrated. All of these impacts from reconfiguration are not uniformly distributed, but fall disproportionately on more rural populations, and the existing evidence base from predominantly metropolitan reconfigurations[5,7] does not allow a precise estimate of the trade-offs at hand when balancing locality against institutional size – a limitation that will hamper professional and public debate regarding the benefits and consequences of large service reorganisations.

In constructing our model, we have assumed all patients will be taken to their closest HASU. If this is not the case (such as decisions being made instead on organisational boundaries) then some inaccuracy of the model around those boundaries is expected. This will be especially true in areas that have more than one HASU in close proximity; in such cases choice of destination may be influenced by factors (such as institutional reputation) other than shortest travel time. With increasing centralisation inaccuracies due to the proximity of units will reduce, as fewer patients will be on the boundary where travel time is not the only influence on the destination. We have also sought to avoid infeasibly large units (those larger than the any existing HASU with more than 2,000 stroke admissions/year), particularly as such an arrangement involves large numbers of stroke-like presentations (‘stroke mimics’) also being conveyed to a HASU – such mimics represent as much as an additional 32% of admissions[26]. Centralisation therefore raises significant issues around the capacity of receiving HASUs, both in infrastructure and workforce. Continued capacity at any HASU will depend on the efficient repatriation to locally-based post-acute and rehabilitation services (e.g. after the first 48-72 hours of care), and we have not modelled these effects or their vulnerability in this paper. There is also uncertainty around the recommended target of 600 admissions per year, not least as random variation would be expected to vary this figure between 550-650 (based on a Poisson distribution). With an ageing population, however, we anticipate a steady increase in admissions to hospital with disabling stroke despite better preventative care, particularly in stroke related to atrial fibrillation[27]. Although such forecasting is imprecise, a potential increase in stroke incidence and hospital admissions could be driven by a predicted 54% increase in the population of England aged 75 or over the next 15 years[28]. Such a rise would militate against enforcing the lower threshold for admissions too strictly (a centre admitting 500 strokes/year at present would very possibly be above that threshold in years to come), and may incline planners to err towards a lower maximum size for any one HASU of say, 1,500 stroke admissions/year, to allow for the projected growth in stroke incidence.

Care should always be taken when considering what appear to be mathematically 'optimal' solutions. A model of this size identifies many solutions that have very similar performance, with only marginal differences between them. Our results are therefore best interpreted as showing the broad number of HASUs that are needed on a national or regional scale to deliver the maximum benefit from centralisation, and what impact this is likely to have on a significant minority of patients. Multiple objective optimisation location problems rarely, if ever, have a single explicit solution, and can illuminate but not dictate regional planning which is still best conducted on a smaller scale, incorporating other local knowledge. Nonetheless, national-level analysis can provide an insight into the range of optimal distributions of stroke centres across England, for which geographical factors are of greater importance than in the predominantly urban reconfigurations that have taken place thus far. For the population of over 8 million people in London, reconfiguration resulted in 8 HASUs with a range of annual stroke admissions between 775 and 1,288 (or 1,023 – 1,700 when FAST-positive stroke mimics are included), and an average ambulance travel time of 17 minutes[2,7]; in Greater Manchester, reconfiguration resulted in 3 HASUs (total stroke admissions between 1,073 and 2,015/year) serving a population of approximately 2.8 million. The national algorithm has identified many possible configurations in which annual admissions to any HASU are within the range 600-2,000 and with at least 80% of patients within 30 minutes of their closest HASU. Choosing between approximately similar options will require other considerations to be taken into account, and this is best performed at a regional level – although not at the relatively small 'footprint' of many of NHS England's 44 Sustainability and Transformation Plans (STPs), the current geographical unit of planning.

Acute stroke care is evolving, and the development of mechanical thrombectomy for acute large artery stroke is likely to create an imperative for still greater centralisation of services[11]. The geographical issues we have identified here will act as an even greater influence on service planning for such specialised treatment, with a similar or more pronounced differential effect between urban and rural environments – removing, for example, the rationale for any metropolitan HASU that is not also capable of delivering mechanical thrombectomy. Further modelling work should be focussed on how best to organise care across England when still greater centralisation of some services are required for a significant proportion of patients.

Conclusions

A policy of centralising acute stroke services across England in 75-85 HASUs could realistically achieve 80-85% of patients attending an acute unit of sufficient size within 30 minutes travel time (with 95% and 98% being within 45 and 60 minutes travel respectively), and with no unit larger than 2,000 stroke admissions per year. Though centralisation could offer significant advantages to the large majority of patients, a small minority (2-4% of the population) would be significantly adversely affected by centralisation, and planning for this minority will inevitably involve compromise between the recommended ideal institutional size and travel times. With centralisation of hyper-acute care, thought also needs to be given to optimal organisation of follow-on care at home or in step-down units, which is beyond the scope of this paper.

What is known already, and what this study adds

What is known already?

NHS England's policy for the centralisation of acute stroke care is based on observational evidence of the mortality benefits from such centralised services, and recommends that all patients should attend a hyperacute stroke unit that both admits at least 600 acute stroke patients per year and is within 30 minutes travel time. Currently just over half (55%) of patients in England receive care at a HASU fulfilling both these conditions.

What this study adds

Applying a multi-objective genetic algorithm approach, we predict that centralising acute stroke services across England in 75-85 HASUs (from the present 127 stroke centres) could realistically achieve all patients attending a stroke unit which has at least 600 acute stroke admissions per year, with 82%, 97% and 99% patients being within 30, 45 and 60 minutes travel respectively. The disbenefit to a significant rural minority is that approximately 7% of patients will move out of a 30 minute travel distance, and an additional 0.7% of patients move out of a 60 minute travel distance.

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References

1 Feigin VL, Forouzanfar MH, Krishnamurthi R, *et al.* Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *Lancet* 2014;**383**:245–55. doi:10.1016/S0140-6736(13)61953-4

2 Sentinel Stroke Audit Programme (SSNAP). Apr2015Mar2016-AnnualResultsPortfolio. Natl. Results April 2015-Mar 2016 https//www.strokeaudit.org/Documents/Results/National/Apr2015Mar2016/Apr2015Mar2016-AnnualResultsPortfolio.aspx. 2016.

3 Newton JN, Briggs ADM, Murray CJL, *et al.* Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;**386**:2257–74. doi:10.1016/S0140-6736(15)00195-6

4 NHS England. Putting Patients First: The NHS business plan 2013/4 - 2015/6. *https://www.england.nhs.uk/wp-content/uploads/2014/04/ppf-1415-1617-wa.pdf* Published Online First: 2013.https://www.england.nhs.uk/wp-content/uploads/2013/04/ppf-1314-1516.pdf

5 Morris S, Hunter RM, Ramsay AIG, *et al.* Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *Bmj* 2014;**349**:g4757–g4757. doi:10.1136/bmj.g4757

6 Hunter RM, Davie C, Rudd A, *et al.* Impact on Clinical and Cost Outcomes of a Centralized Approach to Acute Stroke Care in London: A Comparative Effectiveness Before and After Model. *PLoS One* 2013;**8**:1–9. doi:10.1371/journal.pone.0070420

7 Fulop N, Boaden R, Hunter R, *et al.* Innovations in major system reconfiguration in England: a study of the effectiveness, acceptability and processes of implementation of two models of stroke care. *Implement Sci* 2013;**8**:5. doi:10.1186/1748-5908-8-5

8 Price C, James M. Meeting the Future Challenge of Stroke Meeting the Future Challenge of Stroke. Br. Assoc. Stroke Physicians. 2011.www.basp.ac.uk

9 NHS England. Stroke Services: Configuration Decision Support Guide (www.eoescn.nhs.uk/index.php/download_file/force/2069/168/). 2015.

10 Emberson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from

randomised trials. *Lancet* 2014;**384**:1929–35. doi:10.1016/S0140-6736(14)60584-5

11 Goyal M, Menon BK, Van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;**387**:1723–31. doi:10.1016/S0140-6736(16)00163-X

12 Monks T, Pitt M, Stein K, *et al.* Hyperacute stroke care and NHS England's business plan. *BMJ* 2014;**348**:g3049. doi:10.1136/bmj.g3049

13 Deb K, Pratap A, Agarwal S, *et al.* A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans Evol Comput* 2002;**6**:182–97. doi:10.1109/4235.996017

14 NHS England. Our Business Plan 2016/17. 2016.https://www.england.nhs.uk/wp-content/uploads/2016/03/bus-plan-16.pdf

15 Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke, 5th Edition (Royal College of Physicians of London). 2016.www.strokeaudit.org.uk/guideline (accessed 2 Aug 2017).

16 NHS England. Seven Day Services Clinical Standards. 2017.https://www.england.nhs.uk/wp-content/uploads/2017/02/clinical-standards-feb17.pdf

17 Eissa A, Krass I, Bajorek B V. Barriers to the utilization of thrombolysis for acute ischaemic stroke. *J Clin Pharm Ther* 2012;**37**:399–409. doi:http://dx.doi.org/10.1111/j.1365-2710.2011.01329.x

18 Carter-Jones CR. Stroke thrombolysis: Barriers to implementation. Int. Emerg. Nurs. 2011;**19**:53–7. doi:10.1016/j.ienj.2010.02.005

19 Monks T, Pitt M, Stein K, *et al.* Maximizing the population benefit from thrombolysis in acute ischemic stroke: A modeling study of in-hospital delays. *Stroke* 2012;**43**:2706–11. doi:10.1161/STROKEAHA.112.663187

20 Bray BD, Campbell J, Cloud GC, *et al.* Bigger, faster?: Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke* 2013;**44**:3129–35. doi:10.1161/STROKEAHA.113.001981

21 Strbian D, Ahmed N, Wahlgren N, *et al.* Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry. *Stroke* 2015;**46**:1275–80. doi:10.1161/STROKEAHA.114.007170

22 Ramsay AIG, Morris S, Hoffman A, *et al.* Effects of centralizing acute stroke services on stroke care provision in two large metropolitan areas in England. *Stroke* 2015;**46**:2244–51. doi:10.1161/STROKEAHA.115.009723

23 Mellon L, Doyle F, Rohde D, *et al.* Stroke warning campaigns: delivering better patient outcomes? A systematic review. *Patient Relat Outcome Meas* 2015;**6**:61. doi:10.2147/PROM.S54087

24 Meretoja A, Strbian D, Mustanoja S, *et al.* Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology* 2012;**79**:306–13. doi:10.1212/WNL.0b013e31825d6011

25 Kunz A, Ebinger M, Geisler F, *et al.* Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol* 2016;**15**:1035–43. doi:10.1016/S1474-4422(16)30129-6

26 Dawson A, Cloud GC, Pereira AC, *et al.* Stroke mimic diagnoses presenting to a hyperacute stroke unit. *Clin Med* 2016;**16**:423–6. doi:10.7861/clinmedicine.16-5-423

27 Yiin GSC, Howard DPJ, Paul NLM, *et al.* Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. *J Neurol Neurosurg Psychiatry* 2017;**88**:12–8. doi:10.1136/jnnp-2015-311947

28 Office of National Statistics. Office of National Statistics (2014). 2014-based subnational population projections. 2014.https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/regionsinenglandtable1

Figure legends

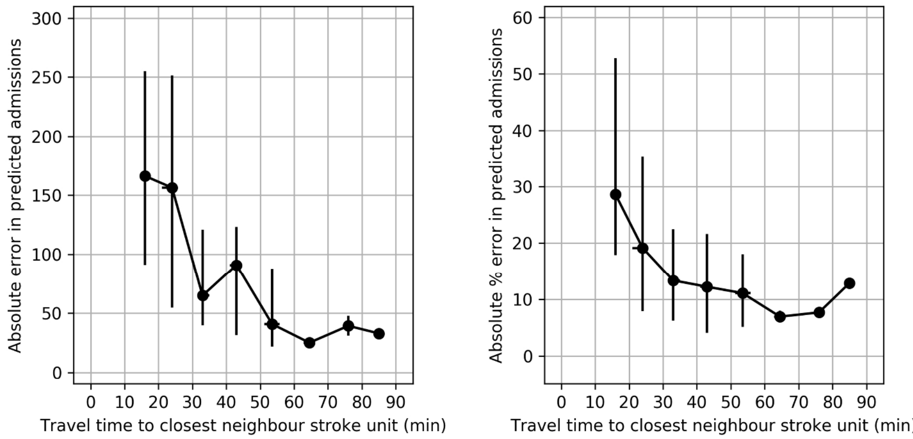
Figure 1. Error in predicting admissions (as recorded in SSNAP) grouped by proximity to the closest neighbouring acute stroke unit (10 minute bins). Points show median with error bars indicating inter-quartile range. The left panel shows the absolute error in predicting admission numbers per year, the right panel shows the absolute error as a percentage of actual admissions for each unit.

Figure 2. The effect of changing the number of acute stroke units on average and maximum travel times. The left panel shows the best average and maximum travel times achieved by the algorithm. The middle panel shows average travel times. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average travel time and other optimisation parameters. The right panel repeats these results for maximum travel time.

Figure 3. The effect of changing the number of acute stroke units on minimum and maximum admissions to any single unit. The left panel shows the best admissions identified by the algorithm (it is better to have a higher minimum number of admissions and lower maximum admissions; that is the smallest hospital should be as large as possible, and the largest hospital as small as possible). The middle panel shows minimum admission numbers (to the smallest unit in each scenario). The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average minimum admissions and other optimisation parameters. The right panel repeats these results for maximum admissions in a scenario.

Figure 4.The effect of changing the number of acute stroke units on the proportion of patients attending a unit with 600 admissions per year, the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location. The top left panel shows the best solutions for each identified by the algorithms. The top right panels shows the proportion of patients attending a unit with 600 admissions per year. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between attending a unit with target admission numbers and other optimisation parameters. The bottom two panels repeat the analysis for the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location.

Figure 5. Histogram of yearly admissions to hospitals. The histogram shows the distribution of admissions across 93 configurations in which annual admissions were kept within 600-2,000 for all units.



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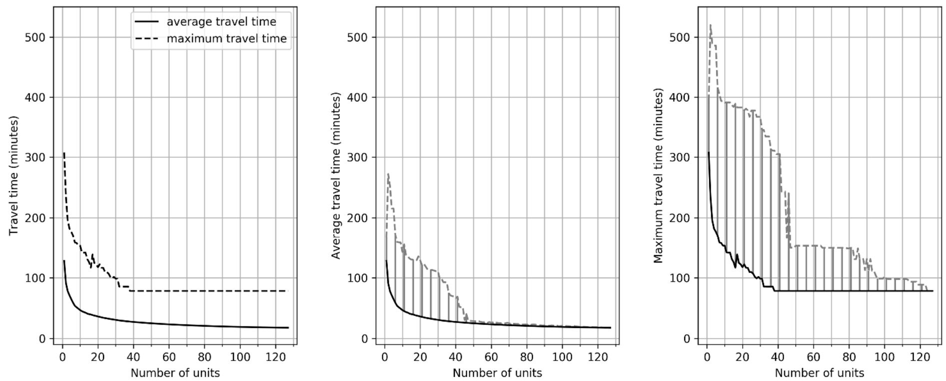

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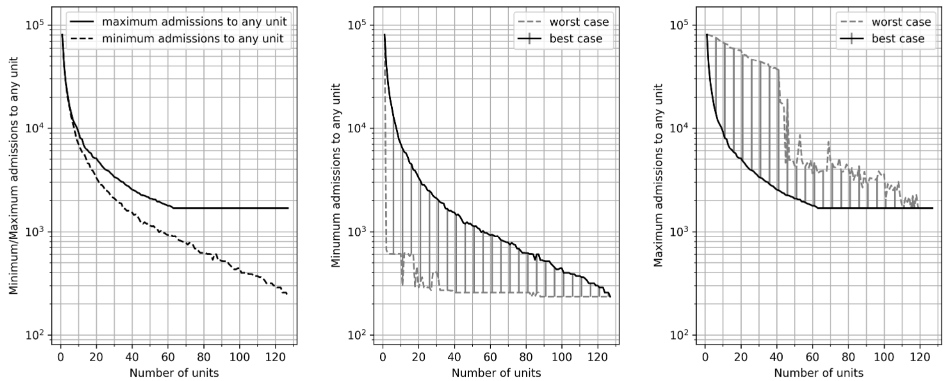

Figure 3. The effect of changing the number of acute stroke units on minimum and maximum admissions to any single unit. The left panel shows the best admissions identified by the algorithm (it is better to have a higher minimum number of admissions and lower maximum admissions; that is the smallest hospital should be as large as possible, and the largest hospital as small as possible). The middle panel shows minimum admission numbers (to the smallest unit in each scenario). The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average minimum admissions and other optimisation parameters. The right panel repeats these results for maximum admissions in a scenario.

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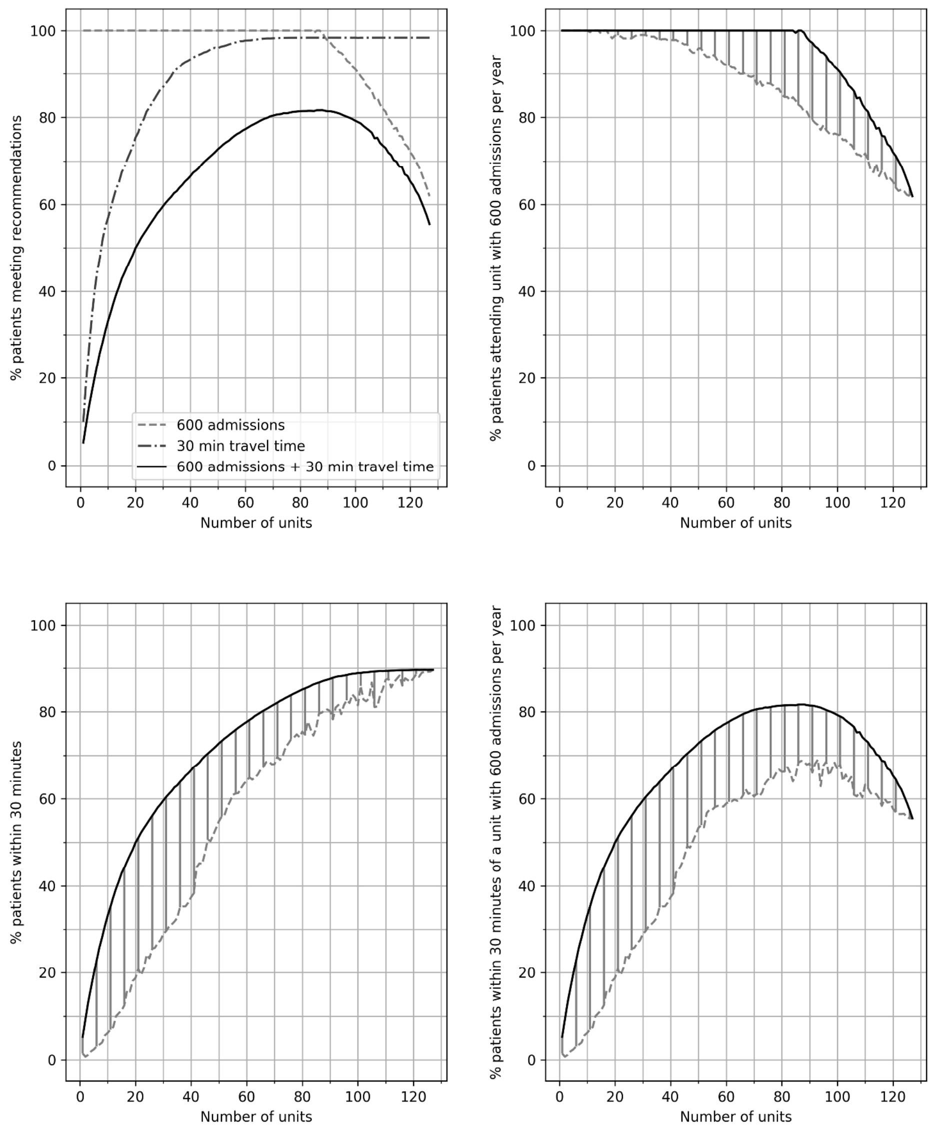

Figure 4.The effect of changing the number of acute stroke units on the proportion of patients attending a unit with 600 admissions per year, the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location. The top left panel shows the best solutions for each identified by the algorithms. The top right panels shows the proportion of patients attending a unit with 600 admissions per year. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between attending a unit with target admission numbers and other optimisation parameters. The bottom two panels repeat the analysis for the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location.

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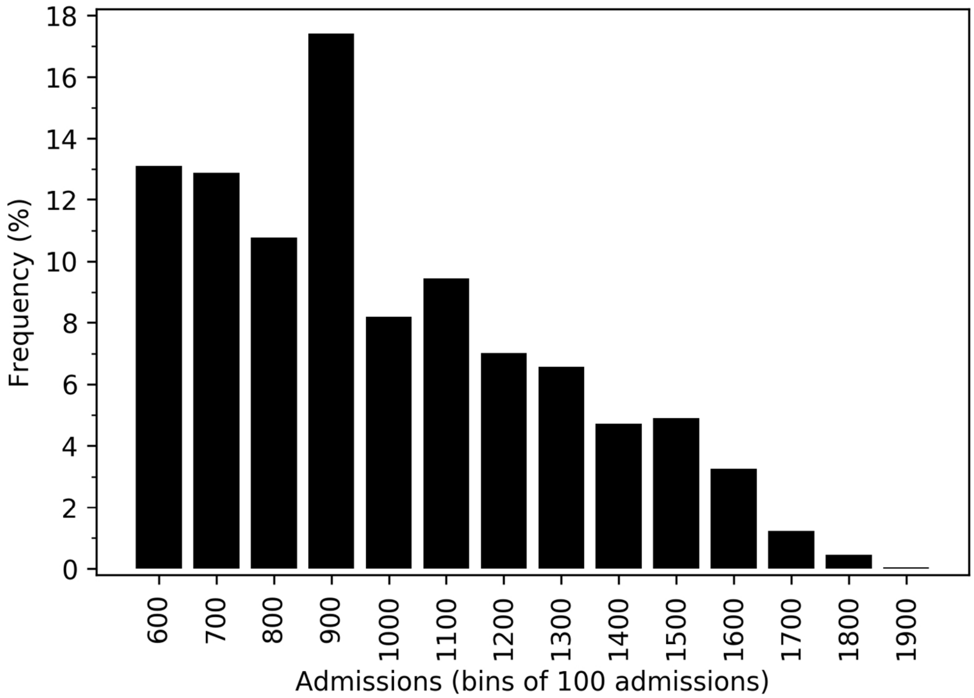

Figure 5. Histogram of yearly admissions to hospitals. The histogram shows the distribution of admissions across 93 configurations in which annual admissions were kept within 600-2,000 for all units.

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Appendix

1 Description of problem

In order to establish a hyper-acute stroke unit (HASU) model for emergency stroke care across England, all HASUs should have a minimum of 6,000 yearly admissions of confirmed strokes. No unit should be infeasibly large (and we have taken the current largest unit with ~2,000 stroke admissions per year as our upper target). All patients are expected to be taken to their closest HASU, with 'closest' chosen by estimated road travel times.

The problem involves looking for solutions that can place any number of hospitals in any of 127 locations. There are therefore 2^127 or 10^38 possible solutions. Each solution requires looking up road travel times from each of 31,171 patient locations to all open hospitals to allocate patients to their closest hospital. There are 13 possible objectives to achieve or trade-off (see section 3.1).

This type of problem is termed 'NP-hard' - it cannot be solved explicitly in reasonable time. And as there are multiple-objectives that trade-off against each other there is no single solution to the problem (as there is no way to objectively determine the weighting of different objectives); rather we are looking for a population of solutions which demonstrate the trade-off between different objectives.

With NP-hard problems there are often a range of different heuristic algorithms which search for good solutions to the problem, while never guaranteeing an optimal solution is found. One set of general purpose heuristic methods are a family of algorithms known as 'genetic algorithms', due to their inspiration coming from the theory of evolution. Here we describe the specific genetic algorithm used in our study.

2 Code and data repository

Data and code used for the model are available at: https://github.com/MichaelAllen1966/stroke_unit_location

Note: The code contains a bespoke Genetic Algorithm written in Python/NumPy. No Genetic Algorithm libraries were used.

3 Multi-objective problem

3.1 Pareto dominance

When solving an optimisation problem based on one objective, the optimal solution is given by the configuration with the best (highest or lowest) objective value. In the case of multi-objective optimisation, comparing several solutions requires to reference to the notion of dominance: a vector $a$of the objective space dominates another vector b if all criteria of a are better or equal to criteria of b and $a \neq b$[1]. Then, a solution is non-dominated if there are no other solutions at least equal in all objectives and better in at least one objective. At the end of the optimisation process, there is no single best solution but a set of non-dominated solutions, called the Pareto Front. An example of a Pareto Front using two objectives is shown in figure 1.

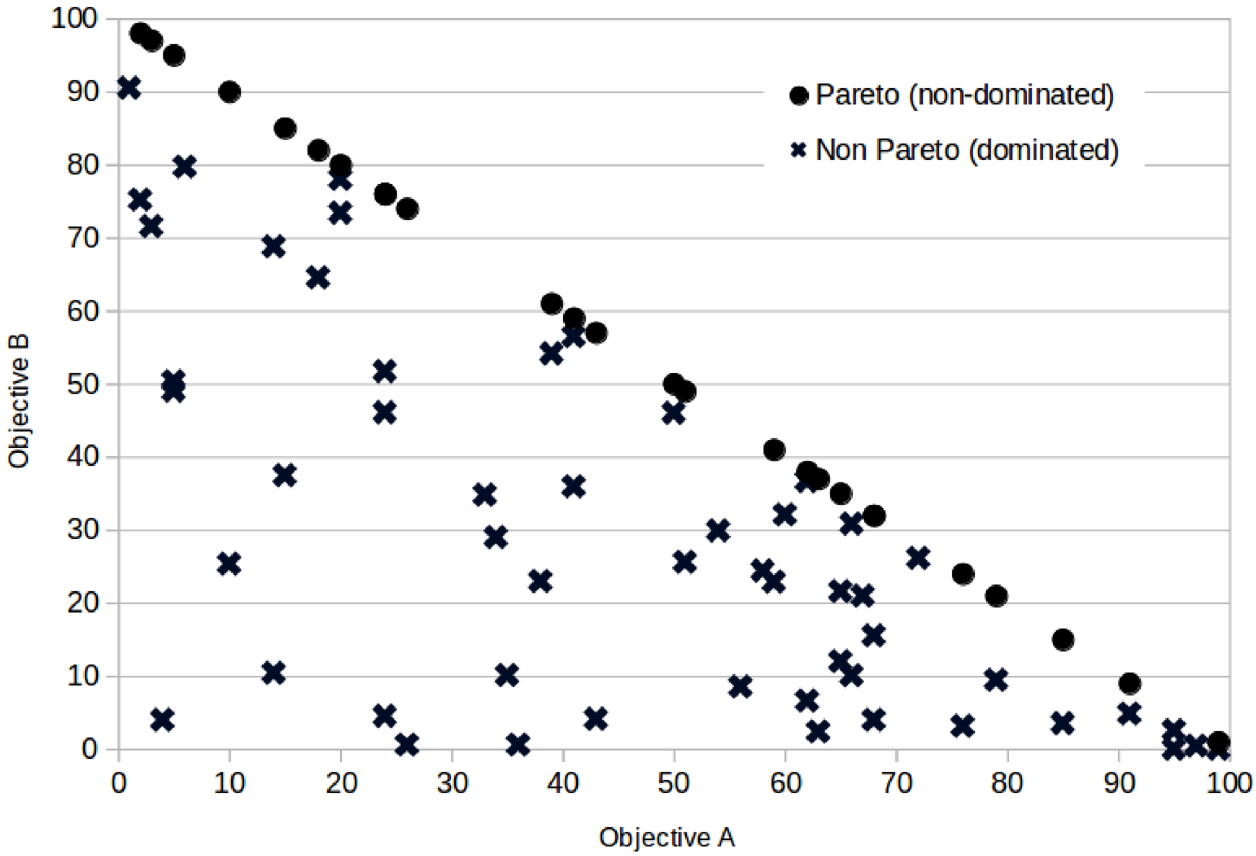

Figure 1: Example of identification of Pareto front (non-dominated) points when comparing two objectives.

The greater the number of objectives on the Pareto Front the lower the chance that a point will be dominated by another. If there is no correlation between objectives and solutions are entirely random then the chance of a single point being dominated by another single point picked at random is 0.5^n_{obj}.

3.2 Algorithm objectives

The objectives which could be used to select solutions were:

1: Number of hospitals (lower is better)

2: Average travel time (lower is better)

3: Maximum travel time (lower is better)

4: Maximum admissions to any one hospital (lower is better)

5: Minimum admissions to any one hospital (higher is better)

6: Max/Min admissions ratio (lower is better)

7: Proportion patients within estimated 30 min travel distance (higher is better)

8: Proportion patients within estimated 45 min travel distance time (higher is better)

9: Proportion patients within estimated 60 min travel distance time (higher is better)

10: Proportion patients attending unit with target admission numbers (higher is better)

11: Proportion patients attending unit with target admission numbers and within estimated 30 min travel time (higher is better)

12: Proportion patients attending unit with target admission numbers and within estimated 45 min travel time (higher is better)

13: Proportion patients attending unit with target admission numbers and within estimated 60 min travel time (higher is better)

Attempting to optimise on all 13 objectives simultaneously produces slow progress. Optimisation on fewer key objectives led to more rapid progress to solutions; these individual solution sets may then be combined and used as a seed for runs with larger numbers of objectives (providing a broader spread of solutions). This progressive extension of objectives is an established general methodology for genetic algorithms [2].

The initial restricted objective runs (focussed on key conflicting priorities) used the following sets of objectives, each of which were aimed at focussing on key trade-offs:

- 1,2,3
- 1,4,5
- 7,10,11
- 8,10,12
- 4,5,7,10,11
- 4,5,8,10,12
- 1,2,4,5,7,10,11
- 1,2,4,5,8,10,12

The advantage of the smaller objective sets is that the chance of Pareto dominance is greater (see section 3.1), leading to greater selection pressures in the algorithm. As an example when starting with a random population of 10,000 solutions the proportion of solutions in the first generation (the randomly chosen generation) that were on the Pareto Front were as follows:

All objectives: Mean 3,295 solutions on Pareto Front (SD =115, n=5)

3 Objectives (8,10,12): Mean 49 solutions on Pareto Front (SD =7, n=5)

Solutions identified from restricted objective runs were combined with solutions identified with runs based on all objectives and were combined into a single Pareto Front. This was used as a seed population for a run based on all objectives.

4 Genetic algorithms

Genetic algorithms manage a population of individuals encoded as vectors through a given number of generations. At each generation, 'good' parents are selected from the population according to their fitness (any measure of superiority over other potential parents). Parents are then combined, using a cross-over operator, to create children which are finally mutated. Genetic algorithms differ in the parent selection process, in the cross-over and mutation processes, and in the way the population is archived.

4.1 Representation

Solutions are coded as binary string of genes with either 1 for an open location or 0 for closed. For instance, 001011 would be six genes that represent hospitals 3, 5 and 6 being open and 1, 2 and 4 being closed. In this study, vectors represent the 127 hospitals (SSNAP acute admitting stroke units).

4.2 Selection

The selection operator chooses a part of the population to become parents. The better individuals in terms of objective values are more likely to become parents. The selection probability can be proportionate to fitness by roulette-wheel sampling[3] or stochastic universal sampling[4]. The sigma scaling method normalises the fitness by its variance in the population, so that the individuals with the highest fitness always have a higher probability than others to produce children. However, these approaches focus on exploitation of existing population rather than exploration of the decision space and they can lead to premature convergence.

Other selection methods rely on ranking rather than fitness value. With ranking selection, individuals are ranked according to their fitness and their probability to become parents is function of their rank[5]. Similarly, the tournament selection creates random pairs of individuals and keeps the one with the highest fitness value with a given probability[3]. Such methods allow the algorithm to keep some individuals with low fitness values (with the advantage of keeping a broader gene pool).

Finally, the Boltzmann selection[6] controls the selection rate via a temperature. At the beginning, all individuals have a similar probability to be selected. As the temperature decreases, the selection focusses on high-fitness individuals.

4.3 Cross-over

The cross-over is the process which exchanges genes from parents to create new children. The simplest option is the single-point cross-over which selects one locus and exchanges the blocks of parents before and after that locus. For instance, a crossover at point five would perform the following:

Parent A: 1 1 1 1 1 1

Parent B: 0 0 0 0 0 0

Child A: = 1 1 1 1 0 0

Child B: 0 0 0 0 1 1

The choice of the single-point location can be made by a uniform distribution. In the case of binary vectors, the single-point cross-over is less likely to exchange the endpoints of vectors [2]. To reduce this effect, the cross-over can rely on two or more exchange points.

4.4 Mutation

Mutation changes the gene value of each locus, with a very small probability for each individual each generation. According to [7], the mutation process avoids the loss of diversity in the population.

4.5 Archive

Genetic algorithms also vary by the way solutions are archived and if the population size is variable. The simple option is to keep only children. However, it assumes that children are better than parents which are lost. Several methods build an archive which is union of parents and children. If the population size is variable, an option is to keep the Pareto Front of this archive. However, the size of this Pareto Front can increase dramatically, in particular with many objective functions. Then, individuals from the archive are ranked, based on their Pareto dominance and another metric. NSGA-II [8] and SPEA2 [9] both rank individuals by combining dominance and spread metric in order to maximise population diversity.

4.6 The NSGA-II method

In NSGA-II [8] the archive and the new population are merged and all individuals are ranked according to a two-step mechanism. In the first step, the merged population is split into layers of non-dominated fronts, the first layer being the Pareto Front (the second layer being the next Pareto Front after removal of the first layer). In the second step, the spread of the population is measured by the crowding distance which gives the distance from an individual to its nearest neighbour. To keep the size of the population constant, a given number of individuals is selected from the merged population, preferably from the upper layers and with the largest crowding distance.

NSGA-II has the advantage to keep not only optimal solutions but also near-optimal solutions in lower layers. However, to do so, the population must be large enough. The second advantage is to provide a diverse population in terms of score values, thanks to the crowding distance ranking.

The NSGA-II was chosen for this study after a pilot comparison with SPEA2[9], MOEAD[10], and HypE[11] which showed that NSGA-II provided similar objective performances with a more diverse population.

4.7 Convergence indicator

Population diversity can be monitored using average Hamming distance. The Hamming distance between any two solutions is the proportion of genes that are different. Average Hamming distance is the mean Hamming distances for all pairwise comparisons in the population (after first Pareto Front selection).

4.8 Description of our genetic algorithm

The Genetic Algorithm used for this study was based on NSGA-II[8]. Our method evolves solutions based on multiple objectives, but without any weighting of objectives. In each generation, the Pareto Front of non-dominated solutions is identified. Larger populations may be selected by picking subsequent Pareto Fronts (re-evaluation the Pareto Front after removal of the previous Pareto Front identified). The population size is maintained in the interval $\left[P_{min}; P_{max}\right]$.

The steps of the algorithm are:

1) Identify which combination of objectives to use for selection in algorithm (may be from 2 objectives to all objectives).

2) Set up initial population of solutions (a typical starting population is 10,000 solutions).

i) Randomly choose number of hospitals to open in each solution.

ii) Randomly assign open hospitals.

iii) A library of solutions may be imported instead of, or in addition to, a random population of solutions.

iv) Non-unique solutions are removed.

3) Breed solutions:

i) Choose pairs of solutions at random from the population.

While NSGA-II selects parents with the tournament method based on weighted criteria, our method selects parents randomly to avoid weighting any objective.

ii) Select a single crossover point at random within the solution binary string.

iii) Apply the cross-over operator to produce children.

iv) Randomly mutate children with a probability per element of 0.002.

v) Combine parents and children into a new population.

vi) Remove non-unique solutions and any solutions where all hospitals are closed.

4) Calculate the performance of all solutions against the objectives used for selection.

5) Identify all non-dominated (Pareto Front) solutions

i) If the number of selected solutions is greater than the maximum permitted population size then reduce the number of solutions by either

(1) picking the required number of solutions at random, or

(2) pick two solutions at random and use tournament selection based on crowding distance

ii) If the number of selected solutions is lower than the target population then remove the previously selected non-dominated solutions and repeat the Pareto selection until sufficient solutions have been identified.

6) Repeat steps 3-5 until the maximum number of generations is reached or the algorithm is stopped by another indicator:

i) Stop the algorithm when there is a change of <0.001 in average Hamming distance across 5 generations.

Note: The minimum and maximum number of solutions to pass on to the next generation may be the same number to keep solution size constant. Alternatively, a range of population size may be acceptable (e.g. a minimum number of 1,000 solutions may be chosen, but a maximum number of 5,000 solutions may be permitted. In this case Pareto selection is repeated until at least 1,000 solutions have been selected, but restriction on the number of solutions only occurs if the number of solutions chosen exceeds 5,000).

The time taken to reach convergence depended on the the number of objectives in the Pareto Front. Typical populations sizes and run times were:

- For 3-4 objectives: population sizes of 2,500 to 5,000 were used. Typical run time to convergence on a single core of a 2GHz processor was 48hrs.
- For 8-12 objectives: population sizes of 5,00 to 10,000 were used. Typical run time to convergence on a single core of a 2GHz processor was 4-7 days.

Note: algorithms may be speeded up by restricting solutions to a smaller range of acceptable number of hospitals (strict filters may be introduced into the algorithm to remove unacceptable solutions before identifying the Pareto Front).

5 References

1 Zhou A, Qu B-Y, Li H, *et al.* Multiobjective evolutionary algorithms: A survey of the state of the art. *Swarm Evol Comput* 2011;**1**:32–49. doi:10.1016/j.swevo.2011.03.001

2 Mitchell M. An introduction to genetic algorithms. *Comput Math with Appl* 1996;**32**:133. doi:10.1016/S0898-1221(96)90227-8

3 Goldberg DE. *Genetic Algorithms in Search, Optimization, and Machine Learning*. 1989. doi:10.1007/s10589-009-9261-6

4 Baker JE. Reducing bias and inefficiency in the selection algorithm. *Proc Second Int Conf Genet Algorithms Genet algorithms their Appl* 1987;:14–21.

5 Baker JE. Adaptive selection methods for genetic algorithms. *Proc an Int Conf Genet Algorithms their Appl* 1985;:101–11.

6 Maza MDA, Tidor B. An analysis of selection procedures with particular attention paid to proportional and Boltzmann selectiono Title. *Proc 5th Int Conf Genet Algorithms* 1993;:124–31.

7 Holland JH. *Adaptation in Natural and Artificial Systems: An introductory Analysis with Applications to Biology, Control and Artificial Intelligence*. 1975. doi:10.1137/1018105

8 Deb K, Pratap A, Agarwal S, *et al.* A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans Evol Comput* 2002;**6**:182–97. doi:10.1109/4235.996017

9 Zitzler E, Laumanns M, Thiele L. SPEA2: Improving the Strength Pareto Evolutionary Algorithm. *Evol Methods Des Optim Control with Appl to Ind Probl* 2001;:95–100. doi:10.1.1.28.7571

10 Zhang Q, Li H. MOEA/D: A multiobjective evolutionary algorithm based on decomposition. *IEEE Trans Evol Comput* 2007;**11**:712–31. doi:10.1109/TEVC.2007.892759

11 Bader J, Zitzler E. HypE: An Algorithm for Fast Hypervolume-Based Many-Objective Optimization. *Evol Comput* 2011;**19**:45–76. doi:10.1162/EVCO_a_00009

STROBE Statement—checklist of items that should be included in reports of observational studies

Please note: The document was written in an Open Office format and saved as a Word document. The page numbers may vary by 1 page depending on the system used to open or process the paper. I've added more detail to the 'Page No. to allow further identification.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 (Title)	Feasibility of a hyper-acute stroke unit model of care across England. A modelling analysis
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3 (Abstract) and 4 (Article Summary)	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 (Intro para 2)	Guidelines recommend a minimum number of admissions to a HASU of 600 patients per year, and NHS England reconfiguration guidelines also suggest 'travel time should be ideally 30 minutes but no more than 60 minutes
Objectives	3	State specific objectives, including any prespecified hypotheses	5 (Intro para 3)	We therefore sought to investigate the potential for meeting the dual objectives of all patients with acute stroke being admitted to a HASU of sufficient size (at least 600 acute stroke patients per year) and that unit being

				within 30 minutes travel time.
Methods				
Study design	4	Present key elements of study design early in the paper	6 (Methods para 2)	The model predicts, for any configuration of HASUs, the travel times (fastest road travel time chosen, from home location of patient to hospital with the shortest estimated travel time), and the number of admissions to each HASU. A genetic algorithm was used to identify good configurations.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 (Methods para 3) Note: this is a modelling study using secondary data only.	We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6 (Methods para 3). Note: this is a modelling study using secondary data only.	We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the		

		number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 (Methods Para 1). Note: this is a modelling study using secondary data only.	The model predicts, for any configuration of HASUs, the travel times (fastest road travel time chosen, from home location of patient to hospital with the shortest estimated travel time), and the number of admissions to each HASU. A genetic algorithm was used to identify good configurations.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 (Methods para 3)	No individual patient level data was accessed: counts of admissions per LSOA were extracted from Hospital Episode Statistics (HES; http://www.hscic.gov.uk/hes) with access to national HES data managed through Lightfoot Solutions (http://www.lightfootsolutions.com/). Estimated fastest road travel times were obtained from a geographic information system (Maptitude, with MP-MileCharter add-in).
Bias	9	Describe any efforts to address potential sources of bias	NA (all confirmed stroke admissions included in analysis)	
Study size	10	Explain how the study size was arrived at	No sampling. All patients with confirmed stroke admitted in England over a 3 year period used.	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable to this modelling study	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Not applicable to this modelling study	
		(*b*) Describe any methods used to examine subgroups and interactions	No subgroups	
		(*c*) Explain how missing data were addressed	No missing data by definition of inclusions (all HES episodes with a primary diagnosis of stroke)	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable: No follow up (modelling study only)	
		(*e*) Describe any sensitivity analyses	Page 9 (Discussion Para 3): discussion of potential impact of ageing population (but not a formal sensitivity analysis)	With an ageing population, however, we anticipate a steady increase in admissions to hospital with disabling stroke despite better preventative care, particularly in stroke related to atrial fibrillation[27]. Although such forecasting is imprecise, a potential increase in stroke incidence and hospital admissions could be driven by a predicted 54% increase in the population of England aged 75 or over the next 15 years
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined	Page 6	We included 238,887 patients

		for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	(Methods para 2)	coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015).
		(b) Give reasons for non-participation at each stage	Not applicable	
		(c) Consider use of a flow diagram	Not applicable as not a trial	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not applicable as modelling study used all emergency stroke admissions in England	
		(b) Indicate number of participants with missing data for each variable of interest	Page 6 (Methods para 2)	We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015).
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable;e: no follow up	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable; not a trial with outcomes	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable; not using sampling	
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7 (Results para 2 et seq). Analysis is on predicted travel times and admissions to hospitals	With an increasing number of HASUs, average and maximum road travel times reduce….
Discussion				
Key results	18	Summarise key results with reference to study objectives	Page 8 (Discussion para 2)	Our modelling of national configurations of HASUs, designed to replicate the population benefits from centralisation of acute stroke services, has shown the feasibility but also the compromises necessary to maximise these benefits. Currently just over half (56%) of patients with acute stroke are admitted to a stroke unit with at least 600 admissions per year[2], and NHS England proposes to increase this proportion through centralisation in fewer, larger units[14]. These HASUs would have staffing levels and competencies as specified in national standards[15,16], and provide intensive (level 2) nursing and medical care for the initial 72 hours after onset (on average) before repatriation of the patient once medically stable to local

				step-down services for ongoing acute care and rehabilitation. By reducing from the current 127 acute sites to between 75-85 HASUs, our centralised HASU model predicts it is possible for all stroke patients to attend a unit of sufficient size, but with a reduction in the proportion of patients within 30 minutes travel from the current 90% to 80-82%, and with 95% and 99% of patients within 45 and 60 minutes travel respectively.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9 (Discussion para 3)	In constructing our model, we have assumed all patients will be taken to their closest HASU. If this is not the case (such as decisions being made instead on organisational boundaries) then some inaccuracy of the model around those boundaries is expected….
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10 (Conclusion)	A policy of centralising acute stroke services across England in 75-85 HASUs could realistically achieve 80-85% of patients attending an acute unit of sufficient size within 30 minutes travel time (with 97% and 98%

				being within 45 and 60 minutes travel respectively), and with no unit larger than 2,000 stroke admissions per year. Though centralisation could offer significant advantages to the large majority of patients, a small minority (2-4% of the population) would be significantly adversely affected by centralisation, and planning for this minority will inevitably involve compromise between the recommended ideal institutional size and travel times.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable, as not trying to extrapolate from trial to full population	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12 (Acknowledgements)	This study was funded by the National Institute of Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care for the South West Peninsula. The views and opinions expressed in this paper are those of the authors, and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Feasibility of a hyper-acute stroke unit model of care across England. A modelling analysis.

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Feasibility of a hyper-acute stroke unit model of care across England. A modelling analysis.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics

This study used aggregate patient counts only, obtained from HES. No individual patient-level data was sought, obtained or used in the study. No ethical approval was sought.

Authorship & contributorship

Michael Allen is the lead author and guarantor, and proposed the key methodology to be used in the study. He also contributed to coding of the model.

Kerry Pearn wrote much of the code used in the model, and contributed to refining the basis of the modelling. She was involved in reviewing and editing the paper.

Emma Villeneuve developed the initial prototypes of the model employed, testing a number of heuristic approaches. She was involved in reviewing and editing the paper.

Thomas Monks framed the initial problem of balancing access to stroke care with developing a unit of sufficient size to maintain expertise, and recommended the modelling study contained herein[1]. He critiqued the methods used in this study, and was involved in reviewing and editing the paper.

Ken Stein oversaw all work. He was involved in framing the problem to be modelled[1]. He critiqued the methods used in this study, and was involved in reviewing and editing the paper.

Martin James is the clinical stroke consultant for the work and paper. He was involved in framing the problem to be modelled[1]. He advised on the clinical objectives of the study, was involved in authoring, reviewing and editing the paper.

1. Monks T, Pitt M, Stein K, et al. Hyperacute stroke care and NHS England's business plan. BMJ 2014;34

Transparancy

The lead author (Michael Allen) confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

Funding

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Data sharing

Full data and code used for this study is available at:
https://github.com/MichaelAllen1966/stroke_unit_location

Included in the data and code are:
Counts of acute stroke admissions by LSOA
Estimated travel times from all LSOAs to all acute stroke units
Hospital information (name, location)
Full source code used to produce results reported here (which runs using open source software)

Abstract

Objectives: The policy of centralising hyperacute stroke units (HASUs) in England aims to provide stroke care in units that are both large enough to sustain expertise (>600 admissions/year) and dispersed enough to rapidly deliver time-critical treatments (<30 minutes maximum travel time). Currently, just over half (56%) of stroke patients access care in such a unit. We sought to model national configurations of HASUs that would optimise both institutional size and geographical access to stroke care, to maximise the population benefit from the centralisation of stroke care.

Design: Modelling of the effect of the national reconfiguration of stroke services. Optimal solutions were identified using a heuristic genetic algorithm.

Setting: 127 acute stroke services in England, serving a population of 54 million people.

Participants: 238,887 emergency admissions with acute stroke over a 3-year period (2013-2015).

Intervention: Modelled reconfigurations of HASUs optimised for institutional size and geographical access.

Main Outcome Measure: Travel distances and times to HASUs, proportion of patients attending a HASU with at least 600 admissions per year, minimum and maximum HASU admissions.

Results: Solutions were identified with 75-85 HASUs with annual stroke admissions in the range 600-2,000, which achieve up to 82% of patients attending a stroke unit within 30 minutes estimated travel time (with at least 95% and 98% patients being within 45 and 60 minutes travel time respectively).

Conclusions: The reconfiguration of hyperacute stroke services in England could lead to all patients being treated in a HASU with between 600 and 2,000 admissions per year. However, the proportion of patients within 30 minutes of a HASU would fall from over 90% to 80-82%.

Article summary

Strengths and weaknesses

- The study described allows for a national view of the relationship between the number of acute stroke units (based on choosing from current locations of acute stroke units) in England and the dual goals of (1) having all patients attend a stroke unit with at least 600 acute confirmed stroke admissions per year, and (2) having patients within 30 minutes of an acute stroke unit.
- The study uses a genetic algorithm that is able to hunt for solutions when there are a vast range of possibilities.
- The study takes an objective approach with explicitly described objectives.
- A limitation of the study is that identified solutions do not take into account the complex local pressures and reasons for preferring one unit over another at the cost of the objectives used in identifying solutions in this study.

Introduction

Stroke is a leading cause of death and disability worldwide, with an estimated 5.9 million deaths and 33 million stroke survivors in 2010[1]. In England, Wales and Northern Ireland 85,000 people are hospitalised with stroke each year[2], and stroke is ranked third as a cause of loss of disability-adjusted life years in the UK over the last 25 years[3].

In recent years the NHS in England has sought to promote the reconfiguration of stroke services across the country, building on the evidence-based model developed in London[4]. Centralisation of stroke care in London has been shown to increase thrombolysis rates, reduce mortality, reduce length of stay, and reduce long-term costs to the NHS[5,6]. These benefits are considered to be due to patients being cared for by specialist stroke teams, facilitated by direct hospital admission to a large hyperacute stroke unit (HASU). In the HASU model of care patients are taken directly to units which may provide immediate response to stroke, including assessment, stabilisation and any primary intervention, before later discharge or transfer to step-down local stroke units[7]. Guidelines recommend a minimum number of admissions to a HASU of 600 patients per year, and NHS England reconfiguration guidelines also suggest 'travel time should be ideally 30 minutes but no more than 60 minutes'[8,9]. Centralisation of acute stroke care in London was guided by a modelling exercise whereby sites were identified with no Londoner more than a 30 minute ambulance journey from the nearest HASU[5]. Time from onset to emergency hospital treatment is known to be especially critical for ischaemic stroke, when the effectiveness of thrombolysis declines rapidly in the first few hours after stroke[10]. More recently, mechanical thrombectomy has shown effectiveness in patients presenting up to 6 hours after stroke onset, with effectiveness still higher if treatment is given earlier[11].

With the critical importance of speed to treatment with thrombolysis or thrombectomy, it has nonetheless been questioned if the improvements in outcome that came with centralisation of stroke services in metropolitan areas could be replicated in more rural environments, with modelling being suggested as a first step at analysing the problem[12]. We therefore sought to investigate the potential for meeting the dual objectives of all patients with acute stroke being admitted to a HASU of sufficient size (at least 600 acute stroke patients per year) and that unit being within 30 minutes travel time. The modelling described here focusses on the Hyper Acute Stroke Unit phase of stroke care[7] and does not extend to organisation of ongoing step-down care in local stroke units, or after discharge home.

Methods

Detailed methods, with links to underlying data and source code used, are given in the on-line appendix.

The model predicts, for any configuration of HASUs, the travel times (fastest road travel time chosen, from home location of patient to hospital with the shortest estimated travel time), and the number of admissions to each HASU. A genetic algorithm was used to identify good configurations.

We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England. No individual patient level data was accessed: counts of admissions per LSOA were extracted from Hospital Episode Statistics (HES; http://www.hscic.gov.uk/hes) with access to national HES data managed through Lightfoot Solutions (http://www.lightfootsolutions.com/). Estimated fastest road travel times were obtained from a geographic information system (Maptitude, with MP-MileCharter add-in).

We used a genetic algorithm based on NSGA-II[13] to derive potential configurations of HASUs across England, balancing competing objectives. Solutions were eliminated if another solution was equally as good in all optimisation parameters and was better in at least one parameter. The selected configurations were based on a range of optimisation parameters (listed in the online appendix) which seek to minimise travel distances and to control admission numbers (admitting as many people to HASUs with at least 600 admissions per year while also seeking to control the maximum number of admissions to any hospital). Solutions retained are referred to as non-dominated solutions; together these form a 'Pareto front' where improved performance in one objective can only be at the expense of another.

Results

The model assumes patients attend the hospital closest to their home location. In order to test this assumption we compared admissions predicted assuming that the closest hospital was used with actual admissions to each hospital. When comparing predicted with actual admissions there was a median absolute error of 105 admissions per unit per year, or a relative absolute error of 17%. Prediction accuracy depended on proximity to a hospital's nearest neighbour, and was proportionately greater in urban areas where travel distance is less of a consideration. HASUs located close to other acutely admitting units have a poorer prediction accuracy than those located further from the nearest alternative acute stroke unit (figure 1). These results gave confidence in progressing with the basic model assumption that patients should generally attend their closest unit.

With an increasing number of HASUs, average and maximum road travel times reduce (figure 2), following the law of 'diminishing returns'. For example, with 24 units (the number of neuroscience centres in England) the lowest average travel time is 34 minutes. As the number of HASUs is increased to 50, 75 and 100, the best average travel times found are 26, 22 and 19 minutes respectively. The best maximum travel time found are 109, 99, 78 and 78 minutes with 25, 50, 75 and 100 HASUs. Average and maximum travel times for the identified solutions depend on what other factors are prioritised in the model. For example, with 25 HASUs, average travel distances in different configurations (all of which are non-dominated solutions) range from 34 to 62 minutes, and maximum travel time range from 109 to 378 minutes.

As the number of HASUs increases, both the maximum and minimum number of admissions to any single hospital in the configuration reduces (figure 3). For example, with 25 units the lowest possible maximum number of admissions to any single unit is 4,381 admissions per year. With 50, 75 and 100 units the largest hospital has admissions of 2,493, 1,829 and 1,687 patients per year. These results represent the best compromise between unit size and distance if no other factors are regarded as important. To achieve all admissions attending a HASU with at least 600 admissions per year the maximum number of hospitals is 85, by which point 82% of the population is within 30 minutes travel (with 95% and 98% being within 45 and 60 minutes, and the maximum travel time is 99 minutes).

As the number of HASUs increases, the proportion of patients within 30 minutes travel increases (figure 4), to a maximum of 90% (the best possible proportions with 25, 50, 75 and 100 units were 52%, 70%, 84% and 88%). At the same time, increasing the number of HASUs reduces the number of patients attending a unit with at least 600 admissions per year (figure 4). Increasing the number of units lead first to an increase in the proportion of patients attending a unit of sufficient size within 30 minutes travel, but when increased further a reduction in this proportion is seen (figure 4). The maximum proportion of patients attending a unit admitting 600 patients per year within 30 minutes travel is 82%. Solutions with at least 80% of patients being within 30 minutes of a HASU admitting at least 600 patients per year have between 75 and 95 HASUs. If target travel time is increased from 30 to 45 minutes then the maximum proportion of patients attending a HASU of sufficient size is 95%, with this maximum occurring with between 65 and 90 units.

In each configuration it may be important to control the maximum number of admissions to any single unit. Configurations of between 75 and 85 HASUs were identified with all patients attending a unit admitting 600 patients per year, at least 80% of patients within 30 minutes travel and maximum admissions to any single HASU of no greater than 2,000. The algorithm identified 93 configurations in which annual admissions were kept within 600-2,000, at least 80% of patients were within 30 minutes of their closest HASU, and at least 95% and 98% of patients were with 45 and 60 minutes of their closest unit. The distribution of size of unit, among all solutions with yearly admissions per unit within the 600 to 2,000 range was skewed significantly towards lower admissions (figure 5), with only 10% of units having more than 1,500 admissions per year.

Discussion

Our modelling of national configurations of HASUs, designed to replicate the population benefits from centralisation of acute stroke services, has shown the feasibility but also the compromises necessary to maximise these benefits. Currently just over half (56%) of patients with acute stroke are admitted to a stroke unit with at least 600 admissions per year[2], and NHS England proposes to increase this proportion through centralisation in fewer, larger units[14]. These HASUs would have staffing levels and competencies as specified in national standards[15,16], and provide intensive (level 2) nursing and medical care for the initial 72 hours after onset (on average) before repatriation of the patient once medically stable to local step-down services for ongoing acute care and rehabilitation. By reducing from the current 127 acute sites to between 75-85 HASUs, our centralised HASU model predicts it is possible for all stroke patients to attend a unit of sufficient size, but with a reduction in the proportion of patients within 30 minutes travel from the current 90% to 80-82%, and with 95% and 98% of patients within 45 and 60 minutes travel respectively.

Maximising the number of patients attending a HASU with at least 600 stroke admissions per year is not an end in itself. The figure is an approximation for the size of a HASU able to develop and sustain expertise in stroke care[9], and overcome identified barriers to improved care such as thrombolysis[17–19]. An association has been observed between door-to-needle time for thrombolysis and institutional size[20,21]. Patients admitted to HASUs in areas that have undergone centralisation were found to be more likely to receive other important clinical interventions such as brain scanning and direct admission to a stroke unit sooner[22]. However, the corollary of such centralisations is the creation of very large units: the most recent Greater Manchester reconfiguration has created one HASU with over 2,000 stroke admissions/year. Our modelling has explored the compromises between institutional size and distance, and the differential effects from centralisation in urban and rural areas. In seeking to balance these often competing priorities, we sought solutions where the largest unit had fewer than 2,000 confirmed stroke admissions per year. We observed that in centralised solutions with all hospital admissions between 600 and 2,000 admissions per year, fewer than 10% of hospitals would have admissions of more than 1,500 per year. Nevertheless, large-scale reconfigurations raise significant issues around the capacity of a small number of very large receiving HASUs, both in infrastructure and workforce, and the potential disbenefits of such large units (if any) are much less well understood. Centralisation to 75-85 hospitals in the manner we have described could therefore be expected to provide a significant benefit to the majority of patients. To yield these benefits, the large majority of patients will travel only moderately further (if at all) to reach a HASU. The disbenefits are to approximately 1.5% of the population who would be more than 60 minutes away from a reconfigured HASU (compared with an estimated 0.3% with all current acute stroke units), and to the 2% of patients who are currently within 30 minutes of an existing centre but who, with centralisation, will travel more than 45 minutes to their nearest HASU. Consideration is therefore needed of how the disbenefits for these patients might be mitigated. Increased travel times might be offset by targeted stroke awareness campaigns (which have been shown to enhance patient response to suspected stroke[23]) leading to earlier contact of emergency services. Increased travel time may also be offset by reduced door-to-treatment time in the HASU[20,24]. More radical solutions for isolated areas include mobile diagnosis and treatment[25]. Early diagnostic access and intravenous thrombolysis is a particular issue given the paucity of geographical coverage of mechanical thrombectomy in the UK, which promotes a model of ‘drip-and-ship’ (near-patient thrombolysis followed by immediate transfer to a more distant thrombectomy centre); currently only 75% of the English population is within 45 minutes travel time of one of the current 24 neurosciences centres, where the expertise in this procedure is exclusively concentrated. All of these impacts from reconfiguration are not uniformly distributed, but fall disproportionately on more rural populations, and the existing evidence base from predominantly metropolitan reconfigurations[5,7] does not allow a precise estimate of the trade-offs at hand when balancing locality against institutional size – a limitation that will hamper professional and public debate regarding the benefits and consequences of large service reorganisations.

In constructing our model, we have assumed all patients will be taken to their closest HASU. If this is not the case (such as decisions being made instead on organisational boundaries) then some inaccuracy of the model around those boundaries is expected. This will be especially true in areas that have more than one HASU in close proximity; in such cases choice of destination may be influenced by factors (such as institutional reputation) other than shortest travel time. With increasing centralisation inaccuracies due to the proximity of units will reduce, as fewer patients will be on the boundary where travel time is not the only influence on the destination. We have also sought to avoid infeasibly large units (those larger than the any existing HASU with more than 2,000 stroke admissions/year), particularly as such an arrangement involves large numbers of stroke-like presentations (‘stroke mimics’) also being conveyed to a HASU – such mimics represent as much as an additional 32% of admissions[26]. Centralisation therefore raises significant issues around the capacity of receiving HASUs, both in infrastructure and workforce. Continued capacity at any HASU will depend on the efficient repatriation to locally-based post-acute and rehabilitation services (e.g. after the first 48-72 hours of care), and we have not modelled these effects or their vulnerability in this paper. There is also uncertainty around the recommended target of 600 admissions per year, not least as random variation would be expected to vary this figure between 550-650 (based on a Poisson distribution). With an ageing population, however, we anticipate a steady increase in admissions to hospital with disabling stroke despite better preventative care, particularly in stroke related to atrial fibrillation[27]. Although such forecasting is imprecise, a potential increase in stroke incidence and hospital admissions could be driven by a predicted 54% increase in the population of England aged 75 or over the next 15 years[28]. Such a rise would militate against enforcing the lower threshold for admissions too strictly (a centre admitting 500 strokes/year at present would very possibly be above that threshold in years to come), and may incline planners to err towards a lower maximum size for any one HASU of say, 1,500 stroke admissions/year, to allow for the projected growth in stroke incidence.

Care should always be taken when considering what appear to be mathematically 'optimal' solutions. A model of this size identifies many solutions that have very similar performance, with only marginal differences between them. Our results are therefore best interpreted as showing the broad number of HASUs that are needed on a national or regional scale to deliver the maximum benefit from centralisation, and what impact this is likely to have on a significant minority of patients. Multiple objective optimisation location problems rarely, if ever, have a single explicit solution, and can illuminate but not dictate regional planning which is still best conducted on a smaller scale, incorporating other local knowledge. Nonetheless, national-level analysis can provide an insight into the range of optimal distributions of stroke centres across England, for which geographical factors are of greater importance than in the predominantly urban reconfigurations that have taken place thus far. For the population of over 8 million people in London, reconfiguration resulted in 8 HASUs with a range of annual stroke admissions between 775 and 1,288 (or 1,023 – 1,700 when FAST-positive stroke mimics are included), and an average ambulance travel time of 17 minutes[2,7]; in Greater Manchester, reconfiguration resulted in 3 HASUs (total stroke admissions between 1,073 and 2,015/year) serving a population of approximately 2.8 million. The national algorithm has identified many possible configurations in which annual admissions to any HASU are within the range 600-2,000 and with at least 80% of patients within 30 minutes of their closest HASU. Choosing between approximately similar options will require other considerations to be taken into account, and this is best performed at a regional level – although not at the relatively small 'footprint' of many of NHS England's 44 Sustainability and Transformation Plans (STPs), the current geographical unit of planning.

Acute stroke care is evolving, and the development of mechanical thrombectomy for acute large artery stroke is likely to create an imperative for still greater centralisation of services[11]. The geographical issues we have identified here will act as an even greater influence on service planning for such specialised treatment, with a similar or more pronounced differential effect between urban and rural environments – removing, for example, the rationale for any metropolitan HASU that is not also capable of delivering mechanical thrombectomy. Further modelling work should be focussed on how best to organise care across England when still greater centralisation of some services are required for a significant proportion of patients.

Conclusions

A policy of centralising acute stroke services across England in 75-85 HASUs could realistically achieve 80-85% of patients attending an acute unit of sufficient size within 30 minutes travel time (with 95% and 98% being within 45 and 60 minutes travel respectively), and with no unit larger than 2,000 stroke admissions per year. Though centralisation could offer significant advantages to the large majority of patients, a small minority (2-4% of the population) would be significantly adversely affected by centralisation, and planning for this minority will inevitably involve compromise between the recommended ideal institutional size and travel times. With centralisation of hyper-acute care, thought also needs to be given to optimal organisation of follow-on care at home or in step-down units, which is beyond the scope of this paper.

What is known already, and what this study adds

What is known already?

NHS England's policy for the centralisation of acute stroke care is based on observational evidence of the mortality benefits from such centralised services, and recommends that all patients should attend a hyperacute stroke unit that both admits at least 600 acute stroke patients per year and is within 30 minutes travel time. Currently just over half (55%) of patients in England receive care at a HASU fulfilling both these conditions.

What this study adds

Applying a multi-objective genetic algorithm approach, we predict that centralising acute stroke services across England in 75-85 HASUs (from the present 127 stroke centres) could realistically achieve all patients attending a stroke unit which has at least 600 acute stroke admissions per year, with 82%, 97% and 99% patients being within 30, 45 and 60 minutes travel respectively. The disbenefit to a significant rural minority is that approximately 7% of patients will move out of a 30 minute travel distance, and an additional 0.7% of patients move out of a 60 minute travel distance.

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References

1 Feigin VL, Forouzanfar MH, Krishnamurthi R, *et al.* Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. *Lancet* 2014;**383**:245–55. doi:10.1016/S0140-6736(13)61953-4

2 Sentinel Stroke Audit Programme (SSNAP). Apr2015Mar2016-AnnualResultsPortfolio. Natl. Results April 2015-Mar 2016 https//www.strokeaudit.org/Documents/Results/National/Apr2015Mar2016/Apr2015Mar2016-AnnualResultsPortfolio.aspx. 2016.

3 Newton JN, Briggs ADM, Murray CJL, *et al.* Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;**386**:2257–74. doi:10.1016/S0140-6736(15)00195-6

4 NHS England. Putting Patients First: The NHS business plan 2013/4 - 2015/6. *https://www.england.nhs.uk/wp-content/uploads/2014/04/ppf-1415-1617-wa.pdf* Published Online First: 2013.https://www.england.nhs.uk/wp-content/uploads/2013/04/ppf-1314-1516.pdf

5 Morris S, Hunter RM, Ramsay AIG, *et al.* Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *Bmj* 2014;**349**:g4757–g4757. doi:10.1136/bmj.g4757

6 Hunter RM, Davie C, Rudd A, *et al.* Impact on Clinical and Cost Outcomes of a Centralized Approach to Acute Stroke Care in London: A Comparative Effectiveness Before and After Model. *PLoS One* 2013;**8**:1–9. doi:10.1371/journal.pone.0070420

7 Fulop N, Boaden R, Hunter R, *et al.* Innovations in major system reconfiguration in England: a study of the effectiveness, acceptability and processes of implementation of two models of stroke care. *Implement Sci* 2013;**8**:5. doi:10.1186/1748-5908-8-5

8 Price C, James M. Meeting the Future Challenge of Stroke Meeting the Future Challenge of Stroke. Br. Assoc. Stroke Physicians. 2011.www.basp.ac.uk

9 NHS England. Stroke Services: Configuration Decision Support Guide (www.eoescn.nhs.uk/index.php/download_file/force/2069/168/). 2015.

10 Emberson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet* 2014;**384**:1929–35. doi:10.1016/S0140-6736(14)60584-5

11 Goyal M, Menon BK, Van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;**387**:1723–31. doi:10.1016/S0140-6736(16)00163-X

12 Monks T, Pitt M, Stein K, *et al.* Hyperacute stroke care and NHS England's business plan. *BMJ* 2014;**348**:g3049. doi:10.1136/bmj.g3049

13 Deb K, Pratap A, Agarwal S, *et al.* A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans Evol Comput* 2002;**6**:182–97. doi:10.1109/4235.996017

14 NHS England. Our Business Plan 2016/17. 2016.https://www.england.nhs.uk/wp-content/uploads/2016/03/bus-plan-16.pdf

15 Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke, 5th Edition (Royal College of Physicians of London). 2016.www.strokeaudit.org.uk/guideline (accessed 2 Aug 2017).

16 NHS England. Seven Day Services Clinical Standards. 2017.https://www.england.nhs.uk/wp-content/uploads/2017/02/clinical-standards-feb17.pdf

17 Eissa A, Krass I, Bajorek B V. Barriers to the utilization of thrombolysis for acute ischaemic stroke. *J Clin Pharm Ther* 2012;**37**:399–409. doi:http://dx.doi.org/10.1111/j.1365-2710.2011.01329.x

18 Carter-Jones CR. Stroke thrombolysis: Barriers to implementation. Int. Emerg. Nurs. 2011;**19**:53–7. doi:10.1016/j.ienj.2010.02.005

19 Monks T, Pitt M, Stein K, *et al.* Maximizing the population benefit from thrombolysis in acute ischemic stroke: A modeling study of in-hospital delays. *Stroke* 2012;**43**:2706–11. doi:10.1161/STROKEAHA.112.663187

20 Bray BD, Campbell J, Cloud GC, *et al.* Bigger, faster?: Associations between hospital thrombolysis volume and speed of thrombolysis administration in acute ischemic stroke. *Stroke* 2013;**44**:3129–35. doi:10.1161/STROKEAHA.113.001981

21 Strbian D, Ahmed N, Wahlgren N, *et al.* Trends in Door-to-Thrombolysis Time in the Safe Implementation of Stroke Thrombolysis Registry. *Stroke* 2015;**46**:1275–80. doi:10.1161/STROKEAHA.114.007170

22 Ramsay AIG, Morris S, Hoffman A, *et al.* Effects of centralizing acute stroke services on stroke care provision in two large metropolitan areas in England. *Stroke* 2015;**46**:2244–51. doi:10.1161/STROKEAHA.115.009723

23 Mellon L, Doyle F, Rohde D, *et al.* Stroke warning campaigns: delivering better patient outcomes? A systematic review. *Patient Relat Outcome Meas* 2015;**6**:61. doi:10.2147/PROM.S54087

24 Meretoja A, Strbian D, Mustanoja S, *et al.* Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology* 2012;**79**:306–13. doi:10.1212/WNL.0b013e31825d6011

25 Kunz A, Ebinger M, Geisler F, *et al.* Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol* 2016;**15**:1035–43. doi:10.1016/S1474-4422(16)30129-6

26 Dawson A, Cloud GC, Pereira AC, *et al.* Stroke mimic diagnoses presenting to a hyperacute stroke unit. *Clin Med* 2016;**16**:423–6. doi:10.7861/clinmedicine.16-5-423

27 Yiin GSC, Howard DPJ, Paul NLM, *et al.* Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. *J Neurol Neurosurg Psychiatry* 2017;**88**:12–8. doi:10.1136/jnnp-2015-311947

28 Office of National Statistics. Office of National Statistics (2014). 2014-based subnational population projections. 2014.https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/regionsinenglandtable1

Figure legends

Figure 1. Error in predicting admissions (as recorded in SSNAP) grouped by proximity to the closest neighbouring acute stroke unit (10 minute bins). Points show median with error bars indicating inter-quartile range. The left panel shows the absolute error in predicting admission numbers per year, the right panel shows the absolute error as a percentage of actual admissions for each unit.

Figure 2. The effect of changing the number of acute stroke units on average and maximum travel times. The left panel shows the best average and maximum travel times achieved by the algorithm. The middle panel shows average travel times. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average travel time and other optimisation parameters. The right panel repeats these results for maximum travel time.

Figure 3. The effect of changing the number of acute stroke units on minimum and maximum admissions to any single unit. The left panel shows the best admissions identified by the algorithm (it is better to have a higher minimum number of admissions and lower maximum admissions; that is the smallest hospital should be as large as possible, and the largest hospital as small as possible). The middle panel shows minimum admission numbers (to the smallest unit in each scenario). The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average minimum admissions and other optimisation parameters. The right panel repeats these results for maximum admissions in a scenario.

Figure 4.The effect of changing the number of acute stroke units on the proportion of patients attending a unit with 600 admissions per year, the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location. The top left panel shows the best solutions for each identified by the algorithms. The top right panels shows the proportion of patients attending a unit with 600 admissions per year. The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between attending a unit with target admission numbers and other optimisation parameters. The bottom two panels repeat the analysis for the proportion of patients attending a unit within 30 minutes of home location and the proportion of patients attending a unit with 600 admissions per year and within 30 minutes of home location.

Figure 5. Histogram of yearly admissions to hospitals. The histogram shows the distribution of admissions across 93 configurations in which annual admissions were kept within 600-2,000 for all units.

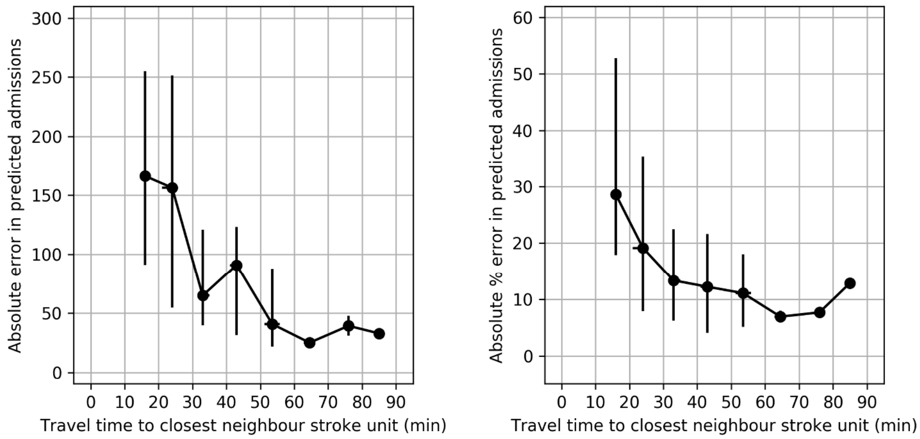

Figure 1. Error in predicting admissions (as recorded in SSNAP) grouped by proximity to the closest neighbouring acute stroke unit (10 minute bins). Points show median with error bars indicating inter-quartile range. The left panel shows the absolute error in predicting admission numbers per year, the right panel shows the absolute error as a percentage of actual admissions for each unit.

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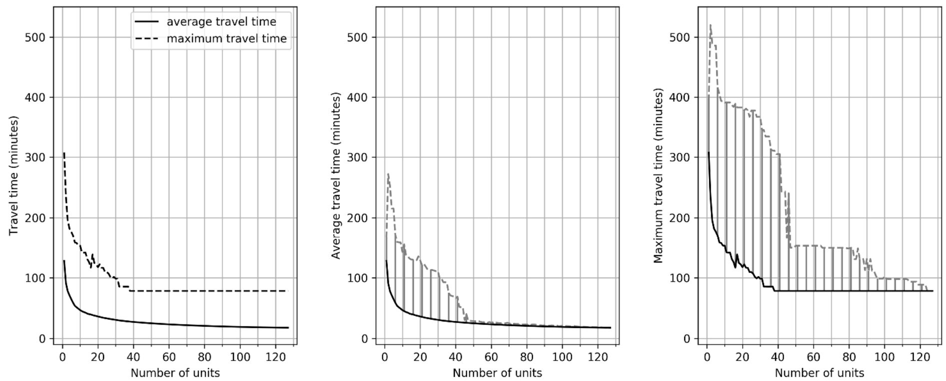

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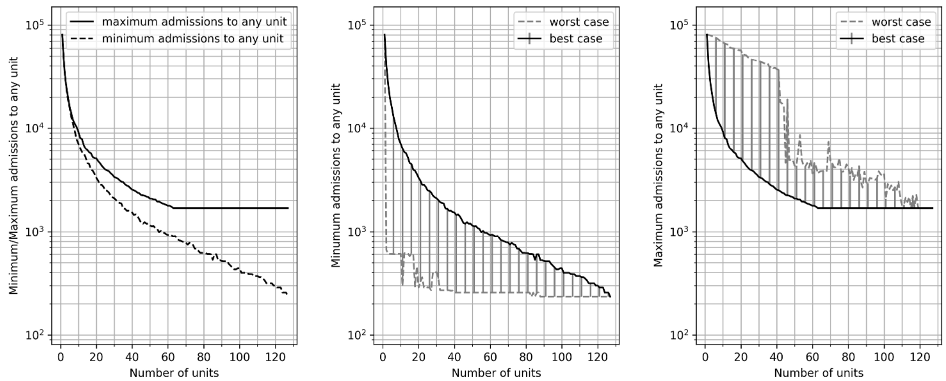

Figure 3. The effect of changing the number of acute stroke units on minimum and maximum admissions to any single unit. The left panel shows the best admissions identified by the algorithm (it is better to have a higher minimum number of admissions and lower maximum admissions; that is the smallest hospital should be as large as possible, and the largest hospital as small as possible). The middle panel shows minimum admission numbers (to the smallest unit in each scenario). The bold line represents the best result identified in any scenario. The dotted line shows the worst result identified for a non-dominated solution. The shaded area represents the effective region of trade-off between average minimum admissions and other optimisation parameters. The right panel repeats these results for maximum admissions in a scenario.

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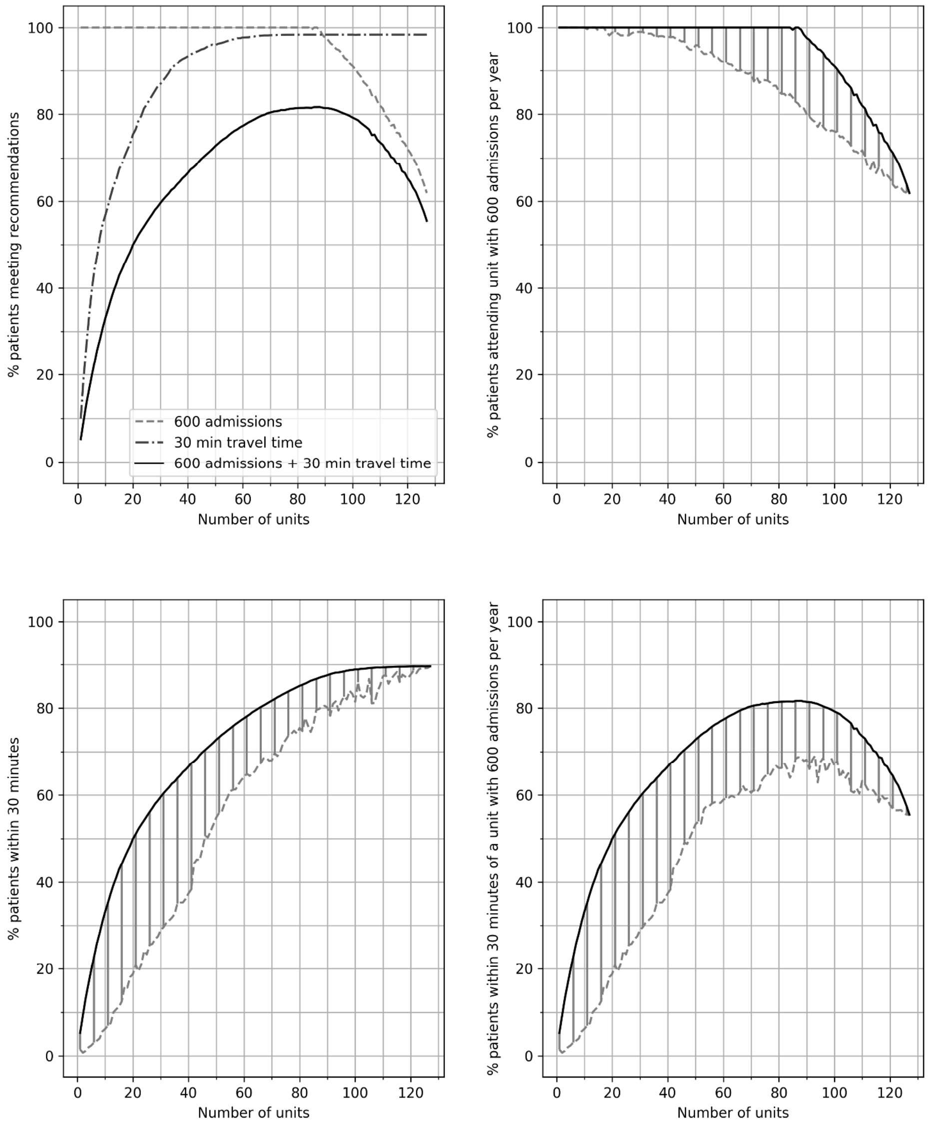

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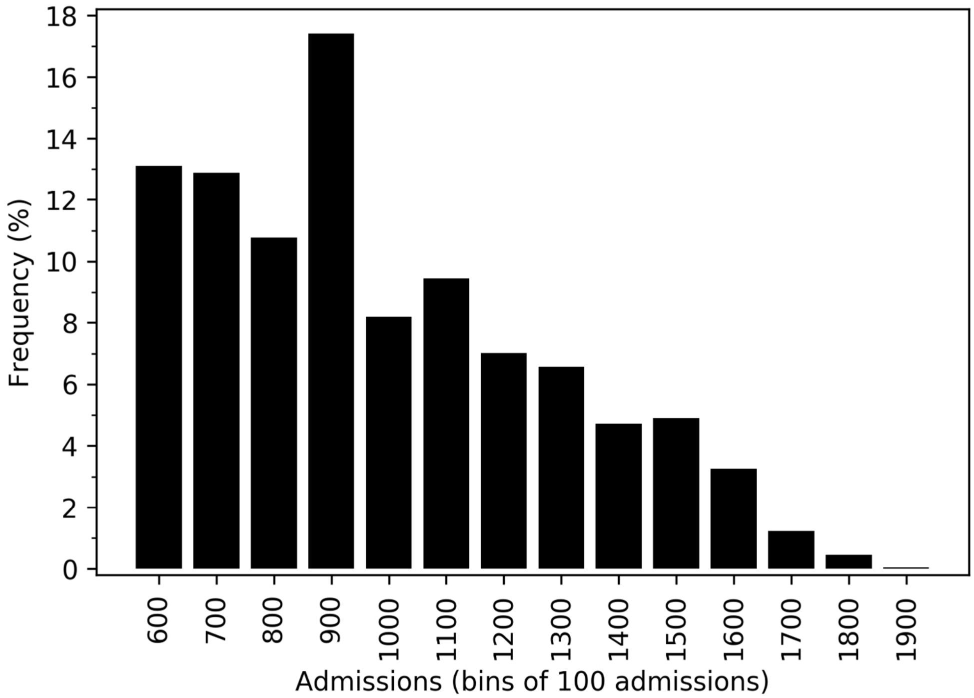

Figure 5. Histogram of yearly admissions to hospitals. The histogram shows the distribution of admissions across 93 configurations in which annual admissions were kept within 600-2,000 for all units.

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Appendix

1 Description of problem

In order to establish a hyper-acute stroke unit (HASU) model for emergency stroke care across England, all HASUs should have a minimum of 600 yearly admissions of confirmed strokes. No unit should be infeasibly large (and we have taken the current largest unit with ~2,000 stroke admissions per year as our upper target). All patients are expected to be taken to their closest HASU, with 'closest' chosen by estimated road travel times.

The problem involves looking for solutions that can place any number of hospitals in any of 127 locations. There are therefore 2^127 or 10^38 possible solutions. Each solution requires looking up road travel times from each of 31,171 patient locations to all open hospitals to allocate patients to their closest hospital. There are 13 possible objectives to achieve or trade-off (see section 3.1).

This type of problem is termed 'NP-hard' - it cannot be solved explicitly in reasonable time. And as there are multiple-objectives that trade-off against each other there is no single solution to the problem (as there is no way to objectively determine the weighting of different objectives); rather we are looking for a population of solutions which demonstrate the trade-off between different objectives.

With NP-hard problems there are often a range of different heuristic algorithms which search for good solutions to the problem, while never guaranteeing an optimal solution is found. One set of general purpose heuristic methods are a family of algorithms known as 'genetic algorithms', due to their inspiration coming from the theory of evolution. Here we describe the specific genetic algorithm used in our study.

2 Code and data repository

Data and code used for the model are available at: https://github.com/MichaelAllen1966/stroke_unit_location

Note: The code contains a bespoke Genetic Algorithm written in Python/NumPy. No Genetic Algorithm libraries were used.

3 Multi-objective problem

3.1 Pareto dominance

When solving an optimisation problem based on one objective, the optimal solution is given by the configuration with the best (highest or lowest) objective value. In the case of multi-objective optimisation, comparing several solutions requires to reference to the notion of dominance: a vector $a$of the objective space dominates another vector b if all criteria of a are better or equal to criteria of b and $a \neq b$[1]. Then, a solution is non-dominated if there are no other solutions at least equal in all objectives and better in at least one objective. At the end of the optimisation process, there is no single best solution but a set of non-dominated solutions, called the Pareto Front. An example of a Pareto Front using two objectives is shown in figure 1.

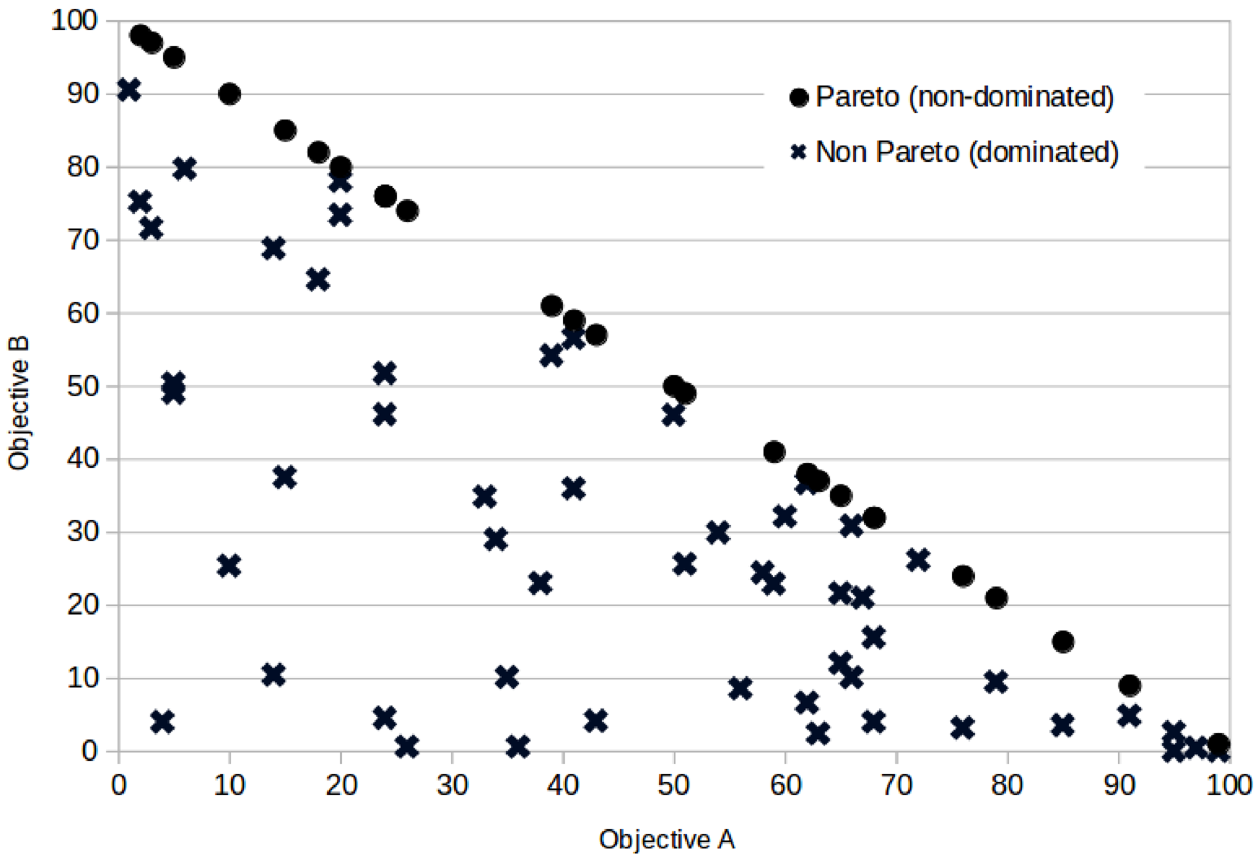

Figure 1: Example of identification of Pareto front (non-dominated) points when comparing two objectives.

The greater the number of objectives on the Pareto Front the lower the chance that a point will be dominated by another. If there is no correlation between objectives and solutions are entirely random then the chance of a single point being dominated by another single point picked at random is $0.5^{\wedge}n_{obj}$.

3.2 Algorithm objectives

The objectives which could be used to select solutions were:

1: Number of hospitals (lower is better)

2: Average travel time (lower is better)

3: Maximum travel time (lower is better)

4: Maximum admissions to any one hospital (lower is better)

5: Minimum admissions to any one hospital (higher is better)

6: Max/Min admissions ratio (lower is better)

7: Proportion patients within estimated 30 min travel distance (higher is better)

8: Proportion patients within estimated 45 min travel distance time (higher is better)

9: Proportion patients within estimated 60 min travel distance time (higher is better)

10: Proportion patients attending unit with target admission numbers (higher is better)

11: Proportion patients attending unit with target admission numbers and within estimated 30 min travel time (higher is better)

12: Proportion patients attending unit with target admission numbers and within estimated 45 min travel time (higher is better)

13: Proportion patients attending unit with target admission numbers and within estimated 60 min travel time (higher is better)

Attempting to optimise on all 13 objectives simultaneously produces slow progress. Optimisation on fewer key objectives led to more rapid progress to solutions; these individual solution sets may then be combined and used as a seed for runs with larger numbers of objectives (providing a broader spread of solutions). This progressive extension of objectives is an established general methodology for genetic algorithms [2].

The initial restricted objective runs (focussed on key conflicting priorities) used the following sets of objectives, each of which were aimed at focussing on key trade-offs:

- 1,2,3
- 1,4,5
- 7,10,11
- 8,10,12
- 4,5,7,10,11
- 4,5,8,10,12
- 1,2,4,5,7,10,11
- 1,2,4,5,8,10,12

The advantage of the smaller objective sets is that the chance of Pareto dominance is greater (see section 3.1), leading to greater selection pressures in the algorithm. As an example when starting with a random population of 10,000 solutions the proportion of solutions in the first generation (the randomly chosen generation) that were on the Pareto Front were as follows:

All objectives: Mean 3,295 solutions on Pareto Front (SD =115, n=5)

3 Objectives (8,10,12): Mean 49 solutions on Pareto Front (SD =7, n=5)

Solutions identified from restricted objective runs were combined with solutions identified with runs based on all objectives and were combined into a single Pareto Front. This was used as a seed population for a run based on all objectives.

4 Genetic algorithms

Genetic algorithms manage a population of individuals encoded as vectors through a given number of generations. At each generation, ‘good’ parents are selected from the population according to their fitness (any measure of superiority over other potential parents). Parents are then combined, using a cross-over operator, to create children which are finally mutated. Genetic algorithms differ in the parent selection process, in the cross-over and mutation processes, and in the way the population is archived.

4.1 Representation

Solutions are coded as binary string of genes with either 1 for an open location or 0 for closed. For instance, 001011 would be six genes that represent hospitals 3, 5 and 6 being open and 1, 2 and 4 being closed. In this study, vectors represent the 127 hospitals (SSNAP acute admitting stroke units).

4.2 Selection

The selection operator chooses a part of the population to become parents. The better individuals in terms of objective values are more likely to become parents. The selection probability can be proportionate to fitness by roulette-wheel sampling[3] or stochastic universal sampling[4]. The sigma scaling method normalises the fitness by its variance in the population, so that the individuals with the highest fitness always have a higher probability than others to produce children. However, these approaches focus on exploitation of existing population rather than exploration of the decision space and they can lead to premature convergence.

Other selection methods rely on ranking rather than fitness value. With ranking selection, individuals are ranked according to their fitness and their probability to become parents is function of their rank[5]. Similarly, the tournament selection creates random pairs of individuals and keeps the one with the highest fitness value with a given probability[3]. Such methods allow the algorithm to keep some individuals with low fitness values (with the advantage of keeping a broader gene pool).

Finally, the Boltzmann selection[6] controls the selection rate via a temperature. At the beginning, all individuals have a similar probability to be selected. As the temperature decreases, the selection focusses on high-fitness individuals.

4.3 Cross-over

The cross-over is the process which exchanges genes from parents to create new children. The simplest option is the single-point cross-over which selects one locus and exchanges the blocks of parents before and after that locus. For instance, a crossover at point five would perform the following:

Parent A: 1 1 1 1 1 1

Parent B: 0 0 0 0 0 0

Child A: = 1 1 1 1 0 0

Child B: 0 0 0 0 1 1

The choice of the single-point location can be made by a uniform distribution. In the case of binary vectors, the single-point cross-over is less likely to exchange the endpoints of vectors [2]. To reduce this effect, the cross-over can rely on two or more exchange points.

4.4 Mutation

Mutation changes the gene value of each locus, with a very small probability for each individual each generation. According to [7], the mutation process avoids the loss of diversity in the population.

4.5 Archive

Genetic algorithms also vary by the way solutions are archived and if the population size is variable. The simple option is to keep only children. However, it assumes that children are better than parents which are lost. Several methods build an archive which is union of parents and children. If the population size is variable, an option is to keep the Pareto Front of this archive. However, the size of this Pareto Front can increase dramatically, in particular with many objective functions. Then, individuals from the archive are ranked, based on their Pareto dominance and another metric. NSGA-II [8] and SPEA2 [9] both rank individuals by combining dominance and spread metric in order to maximise population diversity.

4.6 The NSGA-II method

In NSGA-II [8] the archive and the new population are merged and all individuals are ranked according to a two-step mechanism. In the first step, the merged population is split into layers of non-dominated fronts, the first layer being the Pareto Front (the second layer being the next Pareto Front after removal of the first layer). In the second step, the spread of the population is measured by the crowding distance which gives the distance from an individual to its nearest neighbour. To keep the size of the population constant, a given number of individuals is selected from the merged population, preferably from the upper layers and with the largest crowding distance.

NSGA-II has the advantage to keep not only optimal solutions but also near-optimal solutions in lower layers. However, to do so, the population must be large enough. The second advantage is to provide a diverse population in terms of score values, thanks to the crowding distance ranking.

The NSGA-II was chosen for this study after a pilot comparison with SPEA2[9], MOEAD[10], and HypE[11] which showed that NSGA-II provided similar objective performances with a more diverse population.

4.7 Convergence indicator

Population diversity can be monitored using average Hamming distance. The Hamming distance between any two solutions is the proportion of genes that are different. Average Hamming distance is the mean Hamming distances for all pairwise comparisons in the population (after first Pareto Front selection).

4.8 Description of our genetic algorithm

The code contains a bespoke implementation of a genetic algorithm, based on NSGA-II[8]. Our method evolves solutions based on multiple objectives, but without any weighting of objectives. In each generation, the Pareto Front of non-dominated solutions is identified. Larger populations may be selected by picking subsequent Pareto Fronts (re-evaluation the Pareto Front after removal of the previous Pareto Front identified). The population size is maintained in the interval $\left[P_{min}; P_{max}\right]$.

The steps of the algorithm are:

1) Identify which combination of objectives to use for selection in algorithm (may be from 2 objectives to all objectives).

2) Set up initial population of solutions (a typical starting population is 10,000 solutions).

i) Randomly choose number of hospitals to open in each solution.

ii) Randomly assign open hospitals.

iii) A library of solutions may be imported instead of, or in addition to, a random population of solutions.

iv) Non-unique solutions are removed.

3) Breed solutions:

i) Choose pairs of solutions at random from the population.

While NSGA-II selects parents with the tournament method based on weighted criteria, our method selects parents randomly to avoid weighting any objective.

ii) Select a single crossover point at random within the solution binary string.

iii) Apply the cross-over operator to produce children.

iv) Randomly mutate children with a probability per element of 0.002.

v) Combine parents and children into a new population.

vi) Remove non-unique solutions and any solutions where all hospitals are closed.

4) Calculate the performance of all solutions against the objectives used for selection.

5) Identify all non-dominated (Pareto Front) solutions

i) If the number of selected solutions is greater than the maximum permitted population size then reduce the number of solutions by either

(1) picking the required number of solutions at random, or

(2) pick two solutions at random and use tournament selection based on crowding distance

ii) If the number of selected solutions is lower than the target population then remove the previously selected non-dominated solutions and repeat the Pareto selection until sufficient solutions have been identified.

6) Repeat steps 3-5 until the maximum number of generations is reached or the algorithm is stopped by another indicator:

i) Stop the algorithm when there is a change of <0.001 in average Hamming distance across 5 generations.

Note: The minimum and maximum number of solutions to pass on to the next generation may be the same number to keep solution size constant. Alternatively, a range of population size may be acceptable (e.g. a minimum number of 1,000 solutions may be chosen, but a maximum number of 5,000 solutions may be permitted. In this case Pareto selection is repeated until at least 1,000 solutions have been selected, but restriction on the number of solutions only occurs if the number of solutions chosen exceeds 5,000).

The time taken to reach convergence depended on the the number of objectives in the Pareto Front. Typical populations sizes and run times were:

- For 3-4 objectives: population sizes of 2,500 to 5,000 were used. Typical run time to convergence on a single core of a 2GHz processor was 48hrs.
- For 8-12 objectives: population sizes of 5,00 to 10,000 were used. Typical run time to convergence on a single core of a 2GHz processor was 4-7 days.

Note: algorithms may be speeded up by restricting solutions to a smaller range of acceptable number of hospitals (strict filters may be introduced into the algorithm to remove unacceptable solutions before identifying the Pareto Front).

5 References

1 Zhou A, Qu B-Y, Li H, *et al.* Multiobjective evolutionary algorithms: A survey of the state of the art. *Swarm Evol Comput* 2011;**1**:32–49. doi:10.1016/j.swevo.2011.03.001

2 Mitchell M. An introduction to genetic algorithms. *Comput Math with Appl* 1996;**32**:133. doi:10.1016/S0898-1221(96)90227-8

3 Goldberg DE. *Genetic Algorithms in Search, Optimization, and Machine Learning*. 1989. doi:10.1007/s10589-009-9261-6

4 Baker JE. Reducing bias and inefficiency in the selection algorithm. *Proc Second Int Conf Genet Algorithms Genet algorithms their Appl* 1987;:14–21.

5 Baker JE. Adaptive selection methods for genetic algorithms. *Proc an Int Conf Genet Algorithms their Appl* 1985;:101–11.

6 Maza MDA, Tidor B. An analysis of selection procedures with particular attention paid to proportional and Boltzmann selectiono Title. *Proc 5th Int Conf Genet Algorithms* 1993;:124–31.

7 Holland JH. *Adaptation in Natural and Artificial Systems: An introductory Analysis with Applications to Biology, Control and Artificial Intelligence*. 1975. doi:10.1137/1018105

8 Deb K, Pratap A, Agarwal S, *et al.* A fast and elitist multiobjective genetic algorithm: NSGA-II. *IEEE Trans Evol Comput* 2002;**6**:182–97. doi:10.1109/4235.996017

9 Zitzler E, Laumanns M, Thiele L. SPEA2: Improving the Strength Pareto Evolutionary Algorithm. *Evol Methods Des Optim Control with Appl to Ind Probl* 2001;:95–100. doi:10.1.1.28.7571

10 Zhang Q, Li H. MOEA/D: A multiobjective evolutionary algorithm based on decomposition. *IEEE Trans Evol Comput* 2007;**11**:712–31. doi:10.1109/TEVC.2007.892759

11 Bader J, Zitzler E. HypE: An Algorithm for Fast Hypervolume-Based Many-Objective Optimization. *Evol Comput* 2011;**19**:45–76. doi:10.1162/EVCO_a_00009

STROBE Statement—checklist of items that should be included in reports of observational studies

Please note: The document was written in an Open Office format and saved as a Word document. The page numbers may vary by 1 page depending on the system used to open or process the paper. I've added more detail to the 'Page No. to allow further identification.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 (Title)	Feasibility of a hyper-acute stroke unit model of care across England. A modelling analysis
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3 (Abstract) and 4 (Article Summary)	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5 (Intro para 2)	Guidelines recommend a minimum number of admissions to a HASU of 600 patients per year, and NHS England reconfiguration guidelines also suggest 'travel time should be ideally 30 minutes but no more than 60 minutes
Objectives	3	State specific objectives, including any prespecified hypotheses	5 (Intro para 3)	We therefore sought to investigate the potential for meeting the dual objectives of all patients with acute stroke being admitted to a HASU of sufficient size (at least 600 acute stroke patients per year) and that unit being

				within 30 minutes travel time.
Methods				
Study design	4	Present key elements of study design early in the paper	6 (Methods para 2)	The model predicts, for any configuration of HASUs, the travel times (fastest road travel time chosen, from home location of patient to hospital with the shortest estimated travel time), and the number of admissions to each HASU. A genetic algorithm was used to identify good configurations.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 (Methods para 3) Note: this is a modelling study using secondary data only.	We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6 (Methods para 3). Note: this is a modelling study using secondary data only.	We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015). Stroke admission numbers were counts of admissions for each of 31,771 Lower Super Output Areas (LSOAs) in England.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the		

		number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 (Methods Para 1). Note: this is a modelling study using secondary data only.	The model predicts, for any configuration of HASUs, the travel times (fastest road travel time chosen, from home location of patient to hospital with the shortest estimated travel time), and the number of admissions to each HASU. A genetic algorithm was used to identify good configurations.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 (Methods para 3)	No individual patient level data was accessed: counts of admissions per LSOA were extracted from Hospital Episode Statistics (HES; http://www.hscic.gov.uk/hes) with access to national HES data managed through Lightfoot Solutions (http://www.lightfootsolutions.com/). Estimated fastest road travel times were obtained from a geographic information system (Maptitude, with MP-MileCharter add-in).
Bias	9	Describe any efforts to address potential sources of bias	NA (all confirmed stroke admissions included in analysis)	
Study size	10	Explain how the study size was arrived at	No sampling. All patients with confirmed stroke admitted in England over a 3 year period used.	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Not applicable to this modelling study	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Not applicable to this modelling study	
		(*b*) Describe any methods used to examine subgroups and interactions	No subgroups	
		(*c*) Explain how missing data were addressed	No missing data by definition of inclusions (all HES episodes with a primary diagnosis of stroke)	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable: No follow up (modelling study only)	
		(*e*) Describe any sensitivity analyses	Page 9 (Discussion Para 3): discussion of potential impact of ageing population (but not a formal sensitivity analysis)	With an ageing population, however, we anticipate a steady increase in admissions to hospital with disabling stroke despite better preventative care, particularly in stroke related to atrial fibrillation[27]. Although such forecasting is imprecise, a potential increase in stroke incidence and hospital admissions could be driven by a predicted 54% increase in the population of England aged 75 or over the next 15 years
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined	Page 6	We included 238,887 patients

		for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	(Methods para 2)	coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015).
		(b) Give reasons for non-participation at each stage	Not applicable	
		(c) Consider use of a flow diagram	Not applicable as not a trial	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not applicable as modelling study used all emergency stroke admissions in England	
		(b) Indicate number of participants with missing data for each variable of interest	Page 6 (Methods para 2)	We included 238,887 patients coded with ischaemic or haemorrhagic stroke (ICD-10 I61, I63, I64) with an emergency admission over a three-year period (2013-2015).
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable;e: no follow up	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable; not a trial with outcomes	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable; not using sampling	
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7 (Results para 2 et seq). Analysis is on predicted travel times and admissions to hospitals	With an increasing number of HASUs, average and maximum road travel times reduce….
Discussion				
Key results	18	Summarise key results with reference to study objectives	Page 8 (Discussion para 2)	Our modelling of national configurations of HASUs, designed to replicate the population benefits from centralisation of acute stroke services, has shown the feasibility but also the compromises necessary to maximise these benefits. Currently just over half (56%) of patients with acute stroke are admitted to a stroke unit with at least 600 admissions per year[2], and NHS England proposes to increase this proportion through centralisation in fewer, larger units[14]. These HASUs would have staffing levels and competencies as specified in national standards[15,16], and provide intensive (level 2) nursing and medical care for the initial 72 hours after onset (on average) before repatriation of the patient once medically stable to local

				step-down services for ongoing acute care and rehabilitation. By reducing from the current 127 acute sites to between 75-85 HASUs, our centralised HASU model predicts it is possible for all stroke patients to attend a unit of sufficient size, but with a reduction in the proportion of patients within 30 minutes travel from the current 90% to 80-82%, and with 95% and 99% of patients within 45 and 60 minutes travel respectively.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9 (Discussion para 3)	In constructing our model, we have assumed all patients will be taken to their closest HASU. If this is not the case (such as decisions being made instead on organisational boundaries) then some inaccuracy of the model around those boundaries is expected….
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10 (Conclusion)	A policy of centralising acute stroke services across England in 75-85 HASUs could realistically achieve 80-85% of patients attending an acute unit of sufficient size within 30 minutes travel time (with 97% and 98%

				being within 45 and 60 minutes travel respectively), and with no unit larger than 2,000 stroke admissions per year. Though centralisation could offer significant advantages to the large majority of patients, a small minority (2-4% of the population) would be significantly adversely affected by centralisation, and planning for this minority will inevitably involve compromise between the recommended ideal institutional size and travel times.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Not applicable, as not trying to extrapolate from trial to full population	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12 (Acknowledgements)	This study was funded by the National Institute of Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care for the South West Peninsula. The views and opinions expressed in this paper are those of the authors, and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.