Modelling the resource requirements for implementation of mobile stroke units across the English and Welsh National Health Service, their effectiveness, cost-effectiveness, and their impact upon equity of access to emergency stroke care (MUSTER).

Study protocol

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Version 1

Study applicants

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List of acronyms

AACE	Associate of Ambulance Chief Executives
AIS	Arterial Ischemic Stroke
ASU	Acute Stroke Unit
BIA	Budget Impact Analysis
CSC	Comprehensive Stroke Centre
CT-A	Computed Tomography Angiography
DALY	Disability Adjusted Life Year
EEAST	East of England Ambulance Service NHS Foundation Trust
ESO	European Stroke Organisation
EVT	Endovascular Treatment
FAST	Face, Arm, Speech, Time
GDPR	General Data Protection Regulation
HRA	Health Research Authority
HQIP	Healthcare Quality Improvement Partnership
ICS	Integrated Care System
ISDN	Integrated Stroke Delivery Network
IVT	Intravenous Thombolysis
LSOA	Lower layer Super Output Area
LVO	Large Vessel Occlusion
mRs	modified Rankin scale
MSU	Mobile Stroke Unit
NIHR	National Institute for Health and Care Research
NHS	National Health Service
QALY	Quality Adjusted Life Year
SSNAP	Sentinel Stroke National Audit Programme
UK	United Kingdom

Summary of Research

We will use a sequential equal status approach to developing computer simulation-based models to inform policymakers whether, under what circumstances and when mobile stroke units (MSUs) might be deployed in the English and Welsh National Health Service. The population relevant to our research are suspected stroke patients in England and Wales (most recently observed in 2021 and estimated in 2030) and whose first contact with the acute pathway is outside of hospital. The modelled interventions are acute stroke pathways which include a mobile stroke unit. The modelled comparator is existing acute stroke services and pathways. The outcomes are changes in mortality and dependency, health related quality of life, financial costs and the distribution of access to emergency stroke treatments across the population of suspected stroke patients. The endpoint of our research will be a co-designed and usability-tested web-application for policymakers to use when making decisions about MSUs. The introduction of mobile stroke units will potentially have consequences across the stroke care pathway, from prehospital to rehabilitation. We see identification and estimation of financial consequences to pay for any mobile stroke units, as part of the overall research question. Once estimated, these will form the basis of decisions about whose budget(s) should invest in mobile stroke units. However, it is unlikely that introduction of an MSU by itself would trigger major hospital service reconfiguration.

Because there is limited evidence about the effectiveness of MSUs from the UK NHS, we will model outcomes under two scenarios. The first will be based at Comprehensive Stroke Centres (CSCs) as these were evaluated in trials establishing their effectiveness in non-UK healthcare systems. The second will be based within ambulance services, identified as the most likely scenario for use in the NHS. Developing a likely NHS use scenario through engagement with experts will form one of three workstreams of our proposed research. This may still involve MSUs being based at CSCs but involves a different prehospital pathway and associated resources and costs. Over an 18-month timeframe we will develop geographic and economic models of qualitatively co-designed ambulance service pathway(s) and acute stroke pathways. The co-design and modelling process will be conducted sequentially over four iterations. It will consist of four rounds of workshops with stakeholders, with two separate workshops per round. Stakeholders will include Public and Patient Involvement representees, as well as healthcare professionals and decision makers. The first round of workshops will explore potential ambulance service pathways for MSUs, including feasibility of implementing the models and the identification of relevant outcomes. Remaining workshops will consist of the models being presented back to stakeholders for

discussion and refinement, along with discussion of the mechanism for conveying effects including those on health inequalities. Following the co-design workshops, the mechanism (web application) will be developed, and workshop participants will be invited to test its usability using the 'think-aloud' method, a qualitative approach to usability testing commonly used in the development of digital health interventions [i].

A computer-based, patient level simulation will be developed using most recent and projected incidence of out of hospital stroke. These will include the locations of patients suffering a stroke and facilitate the incorporation of distances and times from care to be included in the models using previously developed models of acute ambulance travel times [ii] [iii]. For current incidence of stroke outside of hospital, we will use data from the Sentinel Stroke National Audit Programme (SSNAP) and update these using estimates of future incidence. Health outcomes will be estimated from differential timings to treatment under the scenarios being compared. The time dependent outcomes of mortality and dependence will be derived from trials of treatments for acute ischaemic stroke treatments [iv] [v]. Health outcomes will be commensurate with these trials and will be in the form of the modified Rankin scale (mRs), the most used outcome measure in stroke clinical trials [vi]. To developed estimates of cost-effectiveness, marginal quality adjusted life year (QALY) estimates will be derived from changes in mRs scores using mappings from a preference-based measure, such as EQ5D [vii]. Changes in distributions of changes in equity of access will be ultimately decided as part of the codesign process, however quantile regression will be used to estimate how MSU have impacted the access [viii]. We will follow the Core20 plus five methodologies to determine how any modelled scenarios impact the most disadvantaged 20% compared to the most advantaged 20% [ix].

For Budget Impact Analysis (BIA) and cost-effectiveness analysis, we will adopt an NHS and social care perspective, modelling extrapolated lifetime outcomes (in the case of cost-effectives analysis) and five-year outcomes in the case of BIA. Relevant good-practice guidance will be followed for modelling and reporting, and all algorithms made available following Open Science principles [x] [xi].

In addition to the web-application that will allow estimation of the local effects of an MSU to be calculated, we also plan a series of dissemination events and academic outputs that will provide more context to policymakers considering the role of MSUs now and in the future within the NHS. In summary, the aim of our research is to inform policymakers about the role that MSUs could play in the NHS regionally and nationally in England and Wales, and the expected health, financial and equity implications. We will do this under a mixed methods paradigm, with ongoing involvement with stakeholders and patient and public representatives who will also provide a critical lens to our data assumptions and research findings.

Background and Rationale

Heightened demographic and fiscal pressures mean the National Health Service (NHS) faces increased demand at the same time as financial and workforce issues constrain supply. When planning services that balance demand and supply in the medium to long term, policymakers are also simultaneously charged with doing so in ways that reduce inequalities within the health and social care system. Relevant research into emerging technologies and service models can inform how these potentially conflicting objectives are met. Patient and public involvement is a key part of informing how our research objectives can address the challenges of evidencing decisions. Mobile Stroke Units (MSU) bring diagnosis and time-critical treatment to the patient instead of transporting them by ambulance to the nearest hospital Acute Stroke Unit (ASU). They offer the prospect of improved health outcomes and consequent significant cost savings. MSUs are ambulances containing specialist equipment, crewed by specialists who can diagnose stroke and initiate time-critical treatment that would otherwise be delayed until patients reach hospital. This treatment is intravenous thrombolysis (IVT). However, despite trial evidence of effectiveness for selected urban populations, there are important resource implications and potential inefficiencies associated with their commissioning and use, which can vary between different settings. For instance, MSU require a stroke specialist physician to confirm the diagnosis and advise on potentially hazardous treatment, and around 50% of the patients attended by an MSU have a non-stroke 'mimic' diagnosis that would usually only require a standard ambulance if diagnosed correctly [xii]. This is an important issue for the NHS which, through necessity, has many smaller ASUs covering more dispersed populations than those in MSU trials. These trials were large urban ASUs with stroke specialists available to maintain a hospital-based service while the MSU was deployed, and UK hospitals do not typically have the capacity to operate acute ambulances. MSUs also offer the prospect of improved outcomes in patents eligible for endovascular treatment (EVT). EVT is a treatment that physically removes the thrombus causing the stroke from the brain, whereas IVT restores blood flow by dissolving the thrombus. Like IVT, it is a time-critical treatment, but is available at a more limited number of specialist units, Comprehensive Stroke Centres (CSCs), in England and Wales. Early diagnosis of stroke by an MSU offers the prospect of directly transporting a patient to a CSC, who otherwise would have been transported to an ASU and then transferred to a CSC.

MSUs have been found to improve functional outcomes in patients with acute ischaemic stroke by reducing delays to treatment and increasing the proportion receiving IVT within 60 minutes from stroke onset. There is also evidence to suggest they are associated with better outcomes for patients with haemorrhagic stroke and increased the numbers of patients being directly transported to specialist centres for EVT. However, only about half of suspected stroke patients are confirmed as having a stroke and not all stroke patients are eligible for treatment, with 80% of patients being ineligible for IVT because of the nature and circumstance of their stroke and 10% of stroke patients are eligible for EVT. The ratio of eligible patients to suspected strokes patients is a determinant of the overall effectiveness and cost-effectiveness of MSUs. When eligibility and ratio of confirmed strokes to suspected stroke are associated with inequalities in access, effectiveness and cost-effectiveness are also therefore associated with inequalities.

A review of the evidence on the effectiveness of MSUs by the European Stroke Organisation (ESO) published in early 2022, suggested MSU management to improve prehospital management of suspected stroke patients [xiii]. It included evidence from three randomised studies [xiv xv xvi] each in Germany and two non-randomised studies from Norway [xvii] and Germany [xviii] . The review concluded that there was a positive effect of MSU versus conventional management on 7-day mortality in patients with suspected acute stroke. For patients with confirmed arterial ischemic stroke (AIS), the review included evidence from three randomised studies [xiv xv xvi], each performed in Germany, and nine non-randomised studies [xix xx xxi xxiii xxii xvv xxvi] into different clinical outcomes conducted in Norway [xvii], Germany [xix xxi xxii xviii], the USA [xx xxiv xxv] and China [xxvi]. The review concluded that when MSUs were compared with conventional management they were "associated with improved functional outcomes, swifter IVT delivery, higher rates of IVT within the golden hour, higher proportion of AIS patients receiving IVT and higher proportion of Large Vessel Occlusion (LVO) patients being primarily transported to tertiary stroke centres".

Why this research is needed now

Despite evidence of effectiveness and ESO recommendations, to date in the UK there are few examples of MSUs. Uncertainty of their effectiveness and cost-effectiveness in a UK context, and financial and human resource constraints are factors in the slow uptake. Evidence from outside the UK suggests MSU can be cost-effective in specific settings. Four studies included in the ESO guidance reported cost effectiveness [xxvii xxviii xxix xxx]. Dietrich et al [xxvii] found, in a German urban context MSUs were cost saving over 12 months based on savings resulting from improved health outcomes because of sooner treatment. They reported these savings were sensitive to the number of staff on the MSU and population density. Gyrd-Hansen et al [xxviii] found that in Germany MSUs were cost effective up to a quality adjusted life year (QALY) threshold of EUR 32,500 in a study based on MSUs. Reimer et al [xxix] reported the results of a cost consequences analysis in a US context. They found that MSUs can avert significant costs associated with the acute stroke pathway once utilisation thresholds are met and significant amongst these cost savings was the secondary transfer of patients. Kim et al [xxx], conducted a cost-effectiveness analysis of an Australian MSU programme and concluded that they were cost effective compared to standard up to a willingness to pay threshold of AUD 31,000 per disability adjusted life year (DALY). That out of the four studies identified, two found that MSUs would be cost saving compared to usual care and two found that this cost-effectiveness was contingent on a notional willingness to pay for a QALY or a DALY, illustrates both the lack of evidence and the context dependency of cost-effectiveness of economic evaluations, as pointed out by Anderson [xxxi]. For MSUs this context is not only made up of demographic factors, geographic factors, the costs of provisions and likely savings from improved outcomes; it also depends on how normal care is constituted.

In addition to the lack of research into their cost-effectiveness within a UK setting that budget holders can call on, it has been argued by Anderson and others that traditional economic evaluations can "*easily be characterised as 'black box' evaluations*" and that "*there is usually neither a clear result that one programme is consistently the most cost-effective in all contexts, nor evidence that can explain how and why the cost-effectiveness of intervention X or programme Y varies so much from context to context*." The purpose of our research is to inform budget holders and policymakers about the costs and gains of MSUs as well as their impact on health inequalities and how context specific factors, such as demographics and population density, affect this information. A 2020 review of the evidence supporting MSUs pointed out their potential impact on inequality, indicating that more remote regions are often less well served, and treatment inequalities are often a result of transport issues, stating 'the value of MSUs, therefore, could be particularly high in such highly disadvantaged regions'. The review cited three studies: One in Germany where selective dispatch of a MSU by means of a patient selection algorithm resulted in a positive predictive value for stroke and suggesting MSUs when dispatched to more remote areas could reduce treatment time [vi]. A second German model study highlighted the disparity between economic and clinical values of MSUs in (geographically) underserved populations [xvi]. The third Canadian study explicitly looked at the effects of MSUs on rural populations, where ambulances met the outbound MSU, and concluded they have potential benefit for remote settings not just in urban settings [xxxii]. Understanding these contextual effects is critical because the effectiveness and cost-effectiveness of MSUs depends on which patients are treated by MSUs and when they are treated, compared to the current local acute stroke services.

Following the release of the ESO recommendations in 2022, those responsible for hyperacute stroke pathways are duty bound to consider the role that mobile stroke units could play. National Clinical Guidelines for Stroke will now be updated with the MSU trials and ESO recommendation, which will lead to each ambulance service and their regional stroke services to consider whether they should introduce an MSU. But evidence of cost-effectiveness in NHS services is lacking. We estimate at a unit cost of £1m/year/MSU based upon descriptions of international services, assuming that there is only one MSU per regional service £15 million could be potentially misallocated away from alternative uses which could offer greater benefits to patients. Except for one service, funding has not yet been committed by regional services because of the lack of evidence of cost-effectiveness and uncertainty about the wider impact on service access. The £15 million therefore represents the maximum Value of Information in reducing decision uncertainty based on the assumption of one MSU per service. For each regional service considering an MSU our research will highlight the trade-offs between financial costs, health outcomes and equity of access.

Research often fails to inform practice, particularly hindered by a lack of consideration for policy processes and policymakers' priorities [xxxiii]. Research approaches from many aligned yet differing fields (for example co-design, usability testing), have increasingly been applied to ensure decision-making is research informed. Examples include co-designing systematic reviews based on usability testing to improve evidence uptake [xxxiv], improving clinical simulations of health information technology [xxxv], and co-designing and usability testing a health analytics platform for consumers and policymakers [xxxvi]. With the arguable exception of the latter study, which focuses on 'big data' rather than health economics, very little research has co-designed economic models, nor fully considered, via co-design and usability testing, how economic models are used in decision-making by policymakers. Our proposed research will evidence from a UK context about whether MSUs dispatched to suspected stroke patients in different settings are cost-effective. It will provide an evidence base to inform policymakers about how MSUs might be deployed within the NHS, the likely health benefits, resource implications and their effects on inequities of access to acute stroke care and health outcomes. Questions about the use of MSUs are being asked at a time when services are facing challenges to meet the aims of the NHS Long Term Plan, one of which is to increase access to EVT [xxxvii]. Because EVT is only performed in specialist CSCs, increasing access means reconfiguring local services around CSCs by either secondary transfer of patients from ASUs to CSC or pre-hospital redirection of patients. We chose to situate our research in the English and Welsh NHS because, as services are currently configured, CSCs in Liverpool and Bristol provide EVT to Welsh patients. Scotland and Norther Ireland were not included because geographic differences would require different modelling techniques. However, many of the algorithms we have developed and propose to develop during this project could be used to model the effects of MSUs in those administrations.

Research into the implications of MSUs compliments previously funded Health and Social Care Delivery Research projects on innovation and implementation of stroke services. There is also helpful overlap between some of this work, for example. CP is chair of the PHOTONIC HSDR evaluation of video triage, which also includes GMc and PMc. We will link directly and to examine the consequences of implementation of outputs from the different projects and share information with the NHSE Ambulance Stroke Working Party chaired by GIRFT Stroke Lead David Hargroves. Our research into the use of MSUs will be framed in the context of previous and current evaluations of reformed care pathways draw on previous work by Prof Fulop and Dr Ramsay. More generally, we are committed to the principles of Open Science and will make publicly available our modelling algorithms to further enhance the knowledge around modelling and evaluating acute stroke services as well as to make research around future evaluations more efficient. There are also currently at least eight ambulance service tele-stroke projects as part of a service improvement initiative funded by NHS England. These are due to report in mid-2023 therefore, we can source original data about call system technical performance, plans for continued use and the triage accuracy to assist with modelling.

The lead applicant (PMc) and the co-applicants (LS, MA, GF, PW, MJ) are current NIHR award holders on the OPTimising IMplementation of Ischaemic Stroke Thrombectomy (OptImIST; NIHR202361) study which aims to identify if and how might ambulance patients be redirected to CSCs in the most effective and cost-effective way. There are synergies between our proposal to evaluate, by modelling, the impact of MSUs in England and Wales with OptImIST which is investigating pre-hospital identification and redirection of patients for IVT. As with OptImIST, the proposed research builds on previous NIHR funded studies into the design of acute stroke services where the applicants are co-investigators (NIHR134326: Stroke Audit Machine Learning (SAMueL-2) NIHR134326 MJ, KP, PMc), (Enhancing and disseminating the outputs of the Promoting Effective and Rapid Stroke Care (PEARS) NIHR PGfAR Programme Grant & facilitating thrombectomy implementation in England NIHR201692 MA, CP, GF, MJ, PMc), (Use of simulation and machine learning to identify key levers for maximising the disability benefit of intravenous thrombolysis in acute stroke pathways (SAMueL) 17/99/89 MA, KP, MJ) (DASH) where expertise and models were developed that will directly inform the proposed research. JS is a Dunhill Medical Trust principal investigator award holder (RPGF2006\226) on a project involving co-designing a system response to safety issues raised during the transition from hospital to care homes, involving an approach akin to the development of our proposed model [xxxviii], and has previously conducted both co-design work with patients and clinicians [xxxix] and qualitative usability testing of a medical device for diagnosing peripheral arterial disease [xl].

Aims and Objectives

The aim of our proposed research is to inform policymakers' decisions about whether to deploy mobile stroke units in the English and Welsh NHS, where they might be deployed, when they might be deployed and what the consequences will be. The study will be organised into three interconnected workstreams (qualitative, quantitative, and economic), with all workstreams contributing to the following objectives:

1. Reach a consensus with stakeholders to define a pre-hospital pathway that includes a mobile stroke unit to parameterise our simulation-based model and appropriately cost the resources required to implement this pathway.
2. Co-produce with stakeholders a simulation-based model based on current stroke incidence and predicted stroke incidence that can be used to estimate the consequences (health-related, financial, and equitable) of deploying mobile stroke units at a sub-national level compared to current service configuration based on national incidence data from SSNAP, travel times obtained from Geographical Information systems and for ambulance data we already have standard approaches for finding suspected stroke cases amongst ambulance records using combinations of 'impression' fields and FAST symptom indicators.
3. Refine the model and its outputs in collaboration with stakeholders to facilitate engagement with the model and its outputs.
4. Through an ongoing process of public and patient engagement, develop a web-based application that can be used to inform local decisions about mobile stroke units and form part of the dissemination activities.

Research Plan and Methods

Research Design

Our research is fully mixed methods. It will use a sequential equal status design that mixes qualitative and quantitative research across each stage of the research process [xli]. The three interconnected workstreams, broadly described as Qualitative, Quantitative and Economic, will be led by JS, MA & PMc, respectively. Over the 18-month timeframe, starting 1st June 2023, we will qualitatively co-produce ambulance service and acute stroke pathways, and co-design appropriate geographic and economic models of these pathways. We describe the research plan and methods below in relation to each workstream, including how they interconnect.

Workstream 1 (Qualitative)

This workstream will contribute to meeting all Objectives and will operate synchronously and in collaboration with the quantitative and economic workstreams. Data will be collected sequentially over four rounds of workshops with stakeholders, including two separate workshops per round. The first round of workshops will explore potential ambulance service pathways for MSUs, including feasibility of implementing the models and the identification of relevant resources and outcomes. This will be done in a manner consistent with the National Institute for Health and Care Excellence's recently published real-world evidence framework [xlii]. With the support of the quantitative and economic workstreams, the remaining workshops will consist of the models being presented back to participants for discussion and refinement, along with discussion of the mechanism for conveying effects on health inequalities. These workshops will link Objective 1 to Objective 2 in our mixed methods paradigm, where co-production of the models is achieved through the collaboration of stakeholders and workstreams.

Participants, sampling, and recruitment

Up to 24 participants per round of workshops will be recruited, with participants split into two separate workshops. Participants will be purposively sampled to represent four key stakeholders: stroke physicians with experience of working in Comprehensive Stroke Centres and/or Acute Stroke Services (n=6), paramedics with stroke expertise (n=6), decision makers (n=6), and stroke-related patient and public representatives (n=6). An additional purposive sampling criterion will include geographical spread. Participants will all be recruited from a variety of established networks outwith the NHS and will be sampled to ensure representation. These will include recruiting Integrated Stroke Delivery Networks (ISDNs), regional networks that aim to share information to provide stroke care, and other relevant stroke special interest groups including the paramedic stroke research group. Patient and public involvement representatives (hereby referred to as stroke representatives) will be recruited via charitable organisations, such as Stroke Association, and/or non-NHS stroke support groups. We will not be recruiting staff or patients via NHS organisations and therefore the study does not require Health Research Authority approval.

The same participants will be invited to participant in all rounds to reduce duplication of discussion, including both the co-design and usability testing, though some attrition is anticipated.

A risk management and mitigation plan will be put in place. Should there be attrition will determine whether attrition is due to unavailability or lack of interest. If unavailability, participants will be offered alternative routes of contributing such as via email, asynchronous remote software (e.g., Miro) or via nominating someone to attend on their behalf. If due to lack of interest or if the prior alternatives are unsuitable resolutions for unavailability, we will recruit a replacement using the original sampling strategy The plan will include that all workshops will be arranged at the outset of the study to best ensure participants are available on future dates. We will also specifically allow for asynchronous data collection and the nomination of deputies. A Quorum will be set specifying necessary attendance levels and minimum representatives per stakeholder. Where quorum is met, but participants unable to attend, we will conduct semi-structured interviews to obtain their perspectives, including reflection on workshop discussions.

Data collection

Each workshop will be hosted online to ensure accessibility [xliii]. Stroke representatives will be provided with the option to attend online, or to accompany the research team face-to-face for a hybrid meeting should they wish to do so, to mitigate the risk of digital exclusion. Stroke representatives will also be offered additional support prior to each workshop so that any technical terms can be explained using lay language, and a glossary of terms will be developed and updated as the project progresses so that they can refer to them at any time. Our PPI co-applicant and the stroke representatives will support us in making any materials aphasia-friendly following the Stroke Association Accessible Information Guidelines [xliv]. Costs have been included for two days per workshop, per participant, as well as travel costs should they be required. At least three members of the research team will attend each workshop to facilitate data collection, including at least one team representative from the qualitative, quantitative, and economic workstreams, to ensure that the co-design work can provide meaningful contribution to the modelling. The presence of representatives from the quantitative and economic workstreams will facilitate the mixed methods approach to meeting Objective 2, which will be led by the quantitative theme, but also involve the economic theme.

Participants will be mixed across specialties and backgrounds in each workshop to ensure discussion of competing opinions, though we will be conscious of perceived power differences and dominating voices that can occur in co-design workshops [xlv]. All workshops will last two hours with breakout sessions included where required. Data will be collected using multiple approaches, including voice recording and transcription of discussions, a Miro interactive whiteboard, and text-based chat features. These approaches will help ensure that quieter voices are heard.

Topic guides will be used to direct the workshop content. Workshop 1 will consist of questions around implementing and operationalising MSUs within an Ambulance Service. This will include topics such as dispatch protocols, staffing, infrastructure costs and relevant potential care pathways by mapping chronological key activities in care processes [xlvi], including for stroke mimics. Engagement with service planners will undoubtedly highlight wider issues around emergency and stroke service reconfigurations, which will be represented in modelling the impact of MSU and we will use the configurations in operation at the time of the modelling to understand what the impact would be. Workshops 2 and 3 will focus predominantly on the geographical and economic modelling questions, including asking participants to weight and rank the relative importance of concepts in the pathway and models. This will consist of Nominal Group Technique including asking participants to score concepts on a five-point Likert scale (least important to most important) so that relevant concepts can be applied to the models. These concepts will likely include the crewing of mobile stroke units, the nature of imaging available on the mobile stroke unit, dispatch protocols, other treatment eligibility criteria, protocols determining which acute stroke unit or comprehensive stroke centre patients should be conveyed to, the effect on patient flows in the acute care sector, and how should stroke mimics and stroke patients who are ineligible for treatment be managed. Participants will also be able to propose additional topics at any stage of the process. Workshop 3 will also include discussion of required web-application features and functionality prioritisation. Workshop 4 will utilise Think Aloud methodology to perform qualitative usability testing of the web-application [xlvii]. Participants will work together in small break-out groups to use the web-application whilst verbalising their thoughts.

Data analysis

Following each workshop, a summary will be produced of relevant concepts and/or adaptations to the models or web-application required, including rankings and/or changes to rankings of priorities. A more in-depth inductive thematic analysis will be conducted following each workshop round, incorporating all the data to provide an audit trail of the co-design process to ensure trustworthiness of the findings. These analyses will help to inform discussion at further workshops and make amendments to the interim modelling and over the course of the process the focus will shift from pathway modelling to results presentation and contextualisation.

Workstreams 2 (Quantitative) and 3 (Economic)

The quantitative and economic workstreams of the research combine with the support of the qualitative theme to achieve Objective 2. As in Objective 1, there will be strong theme of patient involvement through our PPI lead. Meeting Objective 2 begins with developing an initial modelling framework. This occurs concurrently with the initial stage of Objective 1, when the development of an initial Ambulance Service MSU based model begins. This initial modelling framework will identify and collate the key components of the geographic and economics models and deploy them to estimate the marginal effectiveness, cost-effectiveness, budget impact and equity implications of basing mobile stroke units at comprehensive stroke centres. This reflects the scenarios used in the initial trials of mobile stroke units but is not reflective of the UK National Health Service. However, it provides an initial version of the model for development and testing purposes which can then for the basis for engagement and co-production of the model. Taking a lead from Objective 1 we will foster a collaborative approach, explaining initial designs and incorporating thoughts from their own experiences anything that may have omitted, or not thought of as very important.

The core of the research will be the development and refinement (Objective 3) of a computer-based model that will compare how a cohort of suspected stroke patients' outcomes differ between conveyance by standard ambulance to the nearest ASU, in the case of IVT, and in the case of EVT, standard 'Drip and Ship' care, with use of a mobile stroke unit, as described below. The model will reflect the rate at which non-stroke/stroke-mimic callouts need conveyance to hospital, and how that would occur considering Category 2 ambulance response targets. We foresee that non-stroke patients will be an important factor when estimating cost-effectiveness (and effectiveness if they displace and therefore delay treatment of a stroke patient). How stroke mimics (and stroke patients who are ineligible for treatment) are modelled in a pathway, and what the alternatives are, that includes a mobile stroke unit will form a key outcome of engagement with stakeholders in Workstream One.

- *Current provision*: All suspected stroke patients first attend their closest acute stroke unit. Those assessed as suitable for EVT are transferred (if required) to the closest CSC unit.
- *MSUs*: A MSU is dispatched (if available) to suspected stroke patients. For suitable patients, IVT is delivered on-scene. The on-scene scan may also be used to help assess potential suitability for EVT and suitable patients are then taken directly to their closest EVT unit (if different to their closest IVT-capable unit). If identified as a key factor in Objective 1, models will be run comparing whether the MSU has CT (computed tomography) or CT-A (computed tomography angiography); the latter allowing for more certain diagnosis of a large vessel occlusion (LVO) likely to be amenable to EVT).

A schematic of these models of care is shown in figure 1.

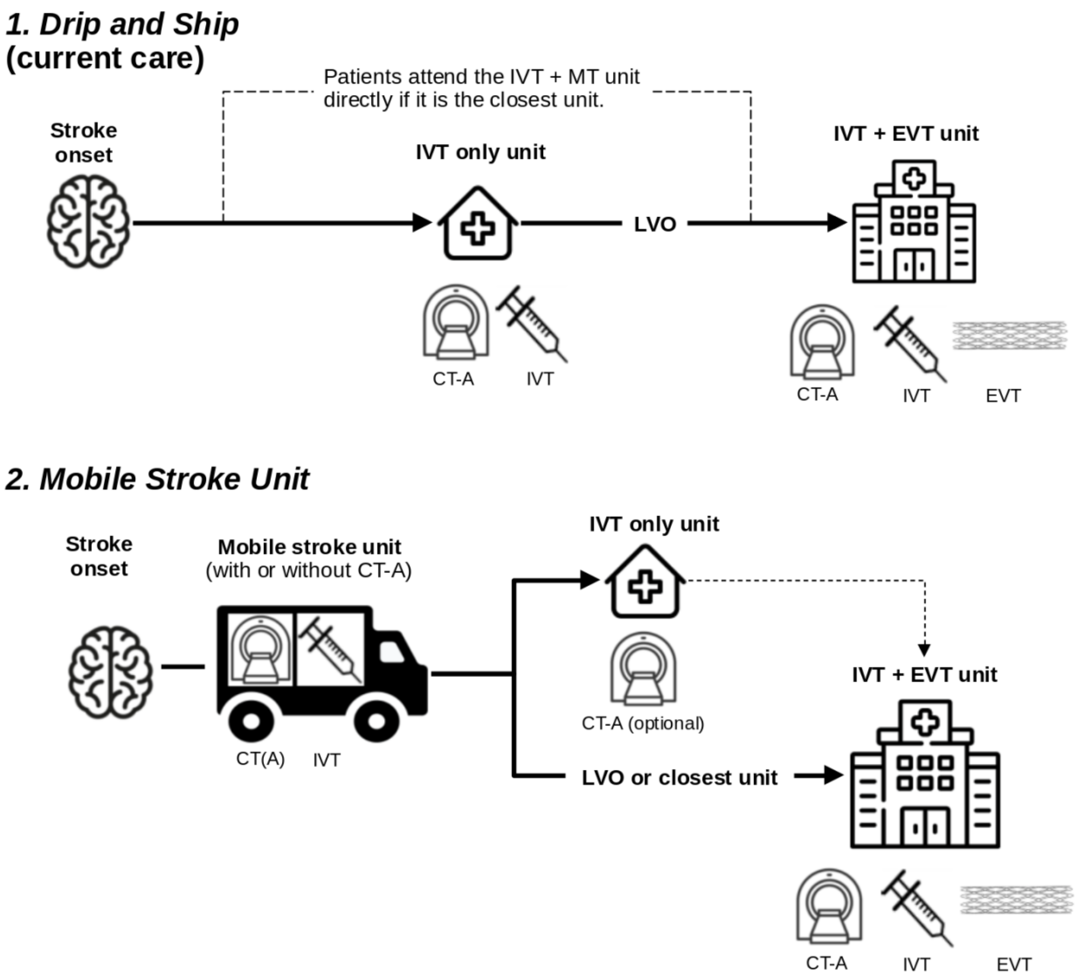


Figure 1: Scenarios to be .

In addition to the key service models, the detailed regional models (see section on Discrete event Simulation below) may also evaluate more complex decision logic, based on feedback received during the co-design workshops facilitated in Objective 1. Examples of more complex models might include:

- Handover of patient from MSU to other ambulance for onward transfer to MT-capable centre (to reduce utilisation of the MSU).
- Use of telemedicine to reduce specialist medical resource time in the MSU.
- Use of pre-hospital diagnostics (e.g., RACE [xlviii]), or a pre-hospital pathway (e.g., NIHR OPTIMIST project)

For modelling we will use national data sets of stroke admission numbers by Lower layer Super Output Area (LSOA). We will access three data sets:

- For stroke admissions by LSOA data in England we have pre-covid HES stroke admission for 2014-1017. This may also be used for future projections based on stratification by age.
- As part of the NIHR SAMueL project we will have admission numbers, times of stroke onset, time to call, time to ambulance arrival, time ambulance on scene, and time to first admitting hospital for all stroke patients 2018-2021. This data will be restricted to admitting hospital but may be used to refine and calibrate ambulance response times in the models.
- We will supplement the above data with a query of national stroke audit data stroke admission counts by LSOA for both England and Wales, and this will cover the years 2016-2021.

- We will build a XGBoost regression model [xlix], linked to a SAHP model that will enhance transparency of the regression model [l], to predict admissions at each LSOA based on future population projections and regional demographics (e.g., Index of Multiple Deprivation). This presents a 'worst case' result where future stroke admissions are not reduced by improved prevention of stroke. The team have experience in using machine learning with stroke admission data [li].

Travel times have been derived from Open Street Map data calibrated against Google maps. We have made estimated travel times from every LSOA to every acute hospital in England (about 5 million combinations) available to others (https://bit.ly/open_travel_times). We will repeat this exercise for Wales.

Sensitivity and specificity of dispatch of an MSU used in our model will be that reported by the East of England Ambulance Service (EEAS). EEAS currently operate an MSU, however data from the service is of limited value in informing our study because the EEAS MSU also responds to non-suspected stroke patients. At this stage we are not aware that any services are considering broadening the scope of mobile stroke units to include non-stroke patients. There is no evidence of their effectiveness or cost-effectiveness based on experimental or quasi-experimental research. East of England Ambulance Service will provide data about the costs of setting up and running the MSU, which will directly inform estimates of cost-effectiveness. Co-Investigator DP will also inform the qualitative workstream in terms of facilitators and barriers for setting up mobile stroke units. For example, in terms of patient handover.

The clinical benefit of MSUs is assessed in the modelling as the number of people achieving threshold disability (mRS) scores, and the shift in mRS scores. These are based on the number of patients treated with IVT and EVT, and the time to treatment with IVT and EVT. We have already developed the core maths and code for estimating stroke outcomes dependent on time to IVT and EVT (all project code will be freely shared for others to use/adapt and is already available at https://samuel-book.github.io/stroke_outcome/

Results (time to first hospital, time to IVT and EVT where appropriate, disability outcomes – health economic outcomes are covered separately) will be broken down by ischaemic stroke types (IVT/EVT eligibility), and on the occurrence of stroke mimics. Further breakdowns of results will be provided. For example, what proportion of ischaemic stroke patients have additional travel time incurred without then receiving IVT and/or MT reperfusion.
Our models will incorporate real world and trial-based estimates of effect wherever possible available in the international publications, or directly from those project teams to calibrate important parameters in the UK model such as geography, population density and stroke service care. These will include data from meta-analyses of time dependent treatments. We will also utilise data from the Sentinel National Stroke Audit Programme to inform estimates of incidence and current time to treatment. Because much of the evidence was not derived from UK based research, we will explicitly consider its relevance to a UK setting. In addition, we will undertake sensitivity analyses around all key model parameters and undertake threshold analyses of key parameters that determine cost-effectiveness.

We will assess placing MSUs at each current emergency stroke unit in isolation to identify individual locations that would lead to most clinical benefit. To examine the best overall coverage of the country for any given number of MSUs we will use “greedy algorithms” and "genetic algorithms" (as we have previously used for maximizing coverage of emergency stroke units). This is necessary, as when two bases for MSUs are close together the coverage from both bases operating together is less than the sum of the two individual hospital coverage areas. Greedy algorithms pick one location at a time that most improves net outcome, and then fixes that position. This is a simple and robust method. Genetic algorithms allow for more flexibility – for example the locations of the best two MSU base locations in any city may not include the location of the first best location chosen by a greedy algorithm.

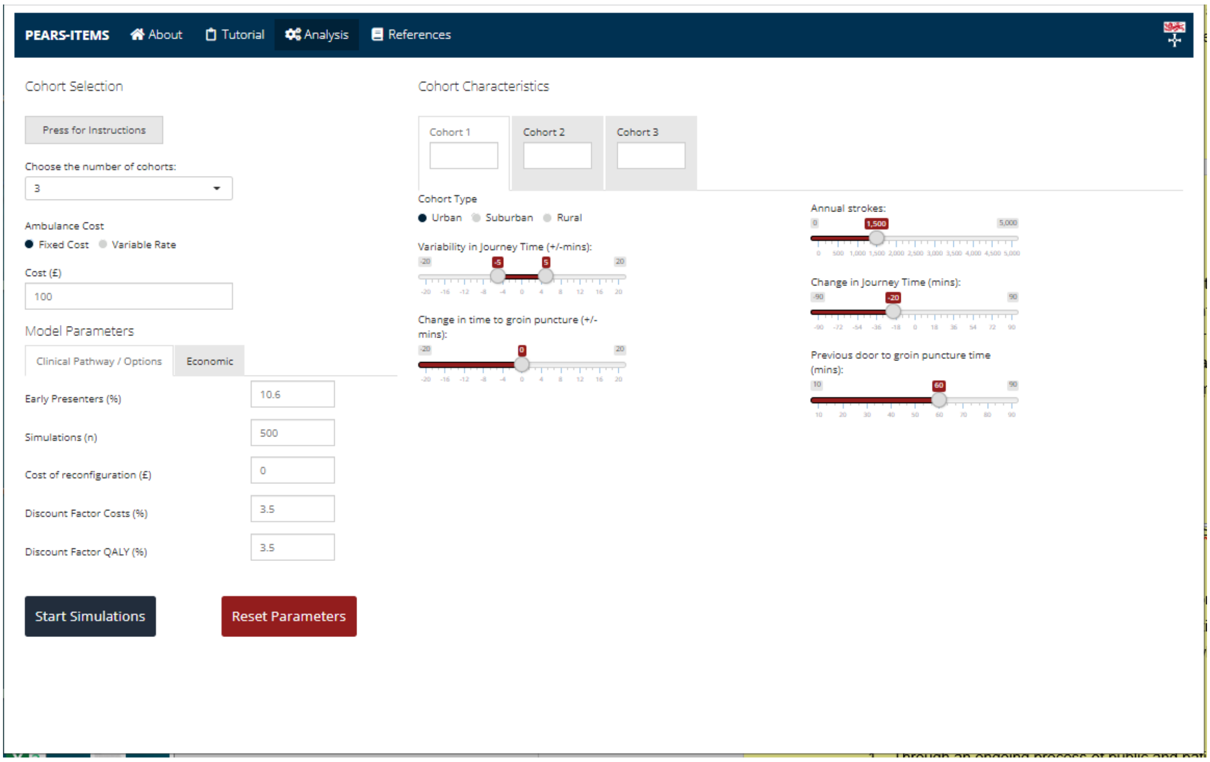
All modelling will be performed in Python, with code made freely available. We have previously published on geographic analysis based on times to treatment with IVT and MT, including the use of pre-hospital diagnostics, and the use of genetic algorithms for optimisation [lii] [xlii] [iii]. This model will be constructed in Python using SimPy as the Discrete Event engine (the team have experience of using SimPy for restricting resources in a stroke system, such as modelling the effect of limited beds in the London acute stroke unit system: https://bit.ly/london_asu).The discrete event model will not only provide an estimate of realistic clinical benefit from MSUs when resources are restricted, but will provide predictions on utilisation of resources, and the effect of altering resources available. The discrete event simulation may also be used to investigate more complex service provision scenarios as outlines above.

The modelling described above has focussed mostly on the effect of different service models on patients – on time to first hospital, on time to reperfusion treatment, and on clinical outcomes. In addition to patient-centric models will we evaluate the effect on emergency and acute resources used as the model is refined (if identified during Objective 3) we will model the amount of emergency ambulance time, MSU time, and transfer ambulance time required with the different service models. We will also estimate the number of admissions and the number of beds required at each hospital for acute stroke care under the three service models.

The estimation of cost effectiveness will be conducted according to best practice [liii]. It will report resources from a health and social care perspective. Resources will include those associated with running the MSU, changes to treatment and any future cost savings. It will take the outputs from the geographic models expressed in changes in numbers of patients in the cohort who achieved each level dependency, as measured by the mRS, and use this information together with information about sex and age to estimate the lifetime changes in costs and QALYs associated with the changes in population dependency associated with the most cost-effective service configurations. QALYs will be based on mortality and utility values derived from the mRS and, as with future costs or savings, be appropriately discounted. This aspect of the sub-theme will report marginal cost effectiveness and associated uncertainty. The second aspect of the health economics theme will be to supply the algorithms to the geographical modelling to theme to estimate the configuration of MSUs based on cost effectiveness metrics. Because the algorithms use preference-based measures to estimate QALYs, the optimal service models may differ from the optimal service models defined in terms of patients treated and mRS scores [iii]. This is important information for policymakers looking to maximise QALYs.

We will assess time to first hospital, time to reperfusion treatment, and clinical outcomes by demographic attributes. This will include Index of Multiple Deprivation [liv lv], and rurality. We will use PPI groups to identify any further groupings where LSOA data is available, for example sub-domains of the IMD.

Web App Through an ongoing process of public and patient engagement develop a web-based application that can be used to inform local decisions about mobile stroke units and form part of the dissemination activities. The underlying basis of the model is benefit for patients through accessing thrombolysis treatment more quickly when symptoms are due to acute ischaemic stroke. To ensure that this is not 'lost' within a description of cost-effectiveness, and so we will also report easily accessible information about the number of patients treated and time to treatment in a way that is informed by our PPI representatives. During the later stages of Objective 3, Objective 4 begins. Taking the key logic of the models and preparing them for use in a web-based application. This application will allow regional decision makers to examine the range of impacts within their region of an MSU. It will allow key parameters to be changed and the effects of MSUs to be captured across a range of outcomes. Once the models have been completed and the forms of outputs agreed (Objective 3), the process of finalising the web-based application will begin. Following the co-design workshops, the mechanism will be developed, and workshop participants will be invited to test its usability using 'think-aloud', a qualitative approach to usability testing commonly used in the development of digital health interventions. Although the final form of the web app is not known, it is likely to follow a similar format to the one developed during the PEARS NIHR Programme Grant for Applied research (https://pears-items.shinyapps.io/PEARS-ITEMS/) . Figure 2. As a web-based application, PEARS-ITEMS, also includes supporting material such as videos to explain how to use the application. The outcome will be a co-designed and usability-tested web-app for policymakers to use when making decisions about MSUs.



The ease of generation of Web Apps has improved radically over the last couple of years, and the team is rapidly building experience in 'StreamLit' Web Apps, to the point that the team is beginning to use them as an easy way for just the team to interactively and dynamically explore modelling results. We will offer each service the results of the relevant regional analysis. Our proposed App would allow decision makers the opportunity to change key model inputs and, we hope, would promote engagement with the research.

Equity considerations

MSUs are most likely to impact geographical inequality of access to acute care through reduced times to diagnosis and treatment. Also inherent in stroke incidence obtained from SSNAP are inequalities associated with geographic location which reflects the risk in the population in that area. Potential benefits of MSUs will be greatest in geographies with higher incidence, all other things being equal. This will be reflected in measures of absolute modelled benefit but may not be captured in our estimates of relative benefits (worst quintile versus best quintile). However, SSNAP does include information about ethnicity (currently 7%-8% specify ‘non-white’). This information together with indices of deprivation at LSOA level will be included in our model to explain modelled benefits. We will also consider in our sensitivity analyses the consequences of thresholds for seeking help by altering the sensitivity and specificity of criteria used to dispatch the mobile stroke unit.

Dissemination, Outputs, and anticipated Impact

We plan to disseminate our outputs through relevant channels including the Stroke Delivery Networks and to the Association of Ambulance Chief Executives (AACE). Each Network will receive a summary of the model estimates for their regional ambulance service. We intend to do this at the same events that the interim outputs from the NIHR OPTIMIST project are delivered. OPTIMIST is concerned with pre-hospital acute stroke pathways, and we will aim to take advantage of this synergy in our dissemination activities. As part of our dissemination activities, we will make all our logic available online in the form of Python code to enable others to utilise in their research projects.

As well as presenting our findings at one national conference – the 2024 UK Stroke Forum, typically held in November, several months after the end of our proposed project, we anticipate three Q1 journal outputs. These would be:

- The results of Objective 1 describing the process and consensus of establishing MSUs in the English and Welsh NHS
- The model results describing the modelled effectiveness of MSU, their cost-effectiveness and likely impact on equity of access now and in 2030.
- The creation of a web-based tool to support policy decisions around MSUs.

We anticipate the impact of our research into MSUs in the UK to be significantly large. Policymakers reacting the European Stroke Associations recommendations are currently facing a dearth of evidence. Any decisions to support MSUs will involve a considerable commitment of resources with unknown outcomes. This uncertainty comes at a time of financial pressures in the NHS and would potentially involve removing or deciding not to fund other activities on the stroke care pathway. The focus on inequality of access and future effects will be relevant to policymakers today looking at inequalities whilst planning care for an increasing number of patients in the future.

Whilst our proposed research focuses on England and Wales, much the material developed could find use in Northern Ireland and Scotland. We will endeavour to share our work with networks in those devolved administrations.

Ethics / Regulatory Approvals

We will comply with all legal and ethical obligations including Data Protection Act 2018, General Data Protection Regulation (GDPR) and the Helsinki Declaration (2013). All necessary ethical approvals will be sought prior to start of data collection, including University ethical approval. Health Research Authority (HRA) approval will not be required based on the HRA decision tool (v2.0, section C1) [lvi] as stroke representatives will not be identified or recruited via NHS services, and stakeholders will be recruited by virtue of their professional role without any material ethical issues, from non-NHS routes. SSNAP data will be accessed through the HQIP approval process. As we are requesting aggregate patient counts only, no ethics approval is required.

Project / research timetable

As the project will require only University Ethics approval because it makes no use of NHS resources, little or no time will need to be spent on governance issues once the project starts. We anticipate applying for permission between the agreement of funding and the project start date. The proposed project will run from April 2023 until September 2024. The qualitative, quantitative, and economic workstreams will run concurrently. While initial specifications of the Ambulance Service based MSU model are being made and processes set up in the qualitative workstream, an initial version of the model will be built by the quantitative and economic workstreams. By month three, the first of four iterative cycles of development will be complete. These will involve further workshops in months beginning in months three, six, nine and will underpin the co-production of the model and the development of the web-application. By month fifteen, we will have a fully functioning model ready to produce results that can be disseminated. The final three months of the project will be spent in dissemination activities and the deployment of the web-based app.

Project Management

PMc will manage the overall project and the health economics workstream. JS and MA will manage the qualitative and quantitative workstreams respectively. The entire project team will meet every two months to review progress. Individual work streams will meet on a minimum of a monthly basis and report back to the project team. We will appoint an independent Project Steering Group who will meet three times during the project in months one, six and fourteen. The Project Steering Group will oversee the research and provide guidance and support across the project lifetime. We will invite the medical director of an ICS to attend Project Steering Group meetings. We will also invite medical directors or research leads from two ambulance services, one that is mainly urban and mainly rural and a specialist in Emergency Medicine to join a Study Advisory Panel.

PPI Lead

Our PPI Lead Mr Dave Wilson is a stroke survivor and a member of a local support group. He will also be a member of the Project Steering groups attend all bi-monthly project team meetings. Mr Wilson formed part of our initial discussions about the project. With the support of Mr Wilson, we will approach the national panel of 10-15 stroke survivors being assembled to provide PPI for the PGfAR OPTIMIST programme which the core team are also delivering to see if they are also willing to provide input for this HSDR. This significantly overlaps because both awards are examining different aspects of emergency stroke care.

"I had a stroke 5 years ago while on a caravan holiday. The cause of the Stroke was a blocked carotid artery on the left side of my neck. I was treated with thrombolysis and discharged after approximately 72 hours. I can't remember this; it is just what I have been told.   Approximately 9 months after my stroke I was medically retired having not been able to return to work.

I started a class called Moving Forward run by the Stroke Association in Gateshead which was a 12-week course attending once a week. I was so impressed by the course that I volunteered to assist in future courses and continued until Covid hit. Unfortunately, the courses stopped and have not started up again, but I still volunteer.

During this time, I worked with the Stroke Association on their publicity work. As part of this I was asked if I would be interested in becoming the Co-Chair of the ISDN Board and leading a group of other stroke survivors and carers in giving patient feedback to the ISDN members regarding the Stroke Process. I have undertaken this role for approximately 18 months."

Success criteria and barriers to proposed work

Our success criteria are proof of influence on national and regional policy decisions. We have sought to minimise risks by not utilising NHS resources at a time when the NHS continues under significant pressures. Recruitment of staff and key staff leaving posts (low likelihood, high impact). If co-applicants change posts, it is likely they will continue with their contribution. If unable, a replacement with suitable skills and knowledge will be invited. Northumbria University has a track record of recruiting high quality researchers. The university has a strong core of research staff that we would be able to access during any transition stages, and applicants from Northumbria University (PMc, JS) line manage several research staff already.

Recruitment of participants to co-design workshops and attrition between workshops (medium likelihood, medium impact). We have developed a robust recruitment strategy that will ensure representation of relevant stakeholders. This recruitment strategy utilises existing links with gatekeepers who are aware of the proposed research and this engagement will continue up until recruitment, for which we have provided sufficient time to recruit participants and schedule workshops. Attrition is possible, but again we have mitigated this risk using various strategies including using suitable deputies, offering asynchronous data collection, and setting clear criteria for replacing participants. Hosting workshops online should also improve access, particularly for clinical staff.

Dominant voices in co-design workshops (high likelihood, medium impact). Bringing together stroke representatives, clinicians from stroke and ambulance services and policymakers is almost certainly going to reinforce existing or create new power dynamics within the workshops. We will mitigate this using various strategies including establishing ground-rules, active facilitation via encouragement of everyone having an opportunity to speak, and use of multiple data collection materials including an interactive whiteboard and in-meeting messaging.

Over-use of technical language (high likelihood, high impact). The development of an ambulance service pathway and modelling work will include the use of technical language that may be difficult for stroke representatives (stroke patients, family members, carers) to engage with, limiting their ability to co-design and inform the research. We have developed a robust strategy for supporting their engagement (see Patient and Public Involvement section of application) including developing a glossary of terms and other materials that are aphasia friendly. We will also regularly liaise with all stroke representatives to discuss how they perceive their ability to contribute and adjust both our engagement strategy and the study design as required to meet these needs.

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