17/99/89: Use of simulation and machine learning to identify key levers for maximising the disability benefit of intravenous thrombolysis in acute stroke pathways (SAMueL)

Protocol V2.0

This merged document (13 March 2020) contains:

File pages 2-25, Section 1: Original Protocol V1.0, 1 March 2019

File pages 26-65, Section 2: Detailed Qualitative Protocol V1.0, 26 September 2019

SECTION 1: ORIGINAL PROTOCOL V1.0
1 MARCH 2019

17/99/89: Use of simulation and machine learning to identify key levers for maximising the disability benefit of intravenous thrombolysis in acute stroke pathways

1. Summary of Research

Background: Stroke is a leading cause of death and disability worldwide. Currently the only licensed drug treatment for acute stroke is thrombolysis with alteplase, the benefit of which is critically time-dependent. There is significant variation between hospitals both in rates of thrombolysis use and door-to-needle times for ischaemic stroke.

Aim: Our aim is to use simulation and machine learning technologies to identify key levers of improvement in thrombolysis use and speed, developing this analysis to be run as part of the routine quarterly national stroke audit. Qualitative research will be undertaken to maximise the acceptance and influence of these techniques.

Methods: Discrete event simulation allows for the prediction of the effect of changing key aspects of the acute stroke pathway (e.g. change in speed). Machine learning techniques allow for an understanding of differences in decision making between different hospitals, and offer the potential for 'exporting' decision making from one location to another. For example, training a machine-learning model based on decision making in a set of benchmark hospitals acknowledged to be centres of clinical excellence, allows an estimation of the effect of similar decision making in different hospitals which might have a different patient mix. All models will be built in Python, allowing easy transfer of techniques. Qualitative research will be based on 1:1 interviews, focus groups and workshops.

Pilot work: Methods have been trialled in seven hospitals in which thrombolysis use for stroke ranged from 7% to 14% of admitted patients. Three factors were pivotal in governing thrombolysis use: (1) the proportion of patients with a known stroke onset time, (2) pathway speed, and (3) predisposition to use thrombolysis for those patients canned with time to treat. A pathway simulation model could predict the potential benefit of improving individual stages of the clinical pathway speed, whereas a machine learning model could predict the benefit of 'exporting' clinical decision making from one hospital to another, whilst allowing for differences in patient population between hospitals. By applying both techniques together, we found a realistic ceiling of 15-25% in use of thrombolysis across different hospitals and more importantly, in the hospitals studied, a realistic opportunity to double the number of patients with no significant disability following treatment with thrombolysis.

Summary of planned work: Models will be refined and developed to run on the national stroke data set as part of routine quarterly audit. This will involve defining a reference group of benchmark hospitals for the decision-making (machine learning model). Pilot work has shown good promise for these techniques, but there is significant scope for optimising models, testing different types of machine learning models, and combining multiple machine learning models. We will pilot different ways of visualising output of models, and conduct qualitative research to understand how best to present model output to maximise their influence and impact in the clinical community.

2. Background and Rationale

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 disability-adjusted life years in the UK over the last 25 years(3). Currently the only licensed drug treatment for acute stroke is thrombolysis with Alteplase, the benefit of which is critically time-dependent(4) with little or no benefit after 4.5 hours from stroke onset. Frustratingly, over the fifteen years since European licencing, the population benefit from thrombolysis has been limited by slow uptake of the treatment, and in-hospital delays to the administration of thrombolysis(5–7).

In England, Wales and Northern Ireland the national stroke audit 'SSNAP' (see below) records that 11.2% of acute stroke patients receive thrombolysis, but use in individual acutely admitting stroke centres varies from 0 to 24.5%(2). The lowest 10% of acutely admitting stroke teams administer thrombolysis to fewer than 5.9% of patients, whereas the top 10% administer thrombolysis to more than 16.7%. Time from arrival to thrombolysis ('door-to-needle') also varies significantly. The fastest 10% of hospitals have door-to-needle times of 40 minutes or less, whereas the slowest 10% have door-to-needle times of 85 minutes or more(2). There is therefore considerable variation between hospitals in the use, and speed, of thrombolysis for acute stroke patients, and the overall use of thrombolysis and the high inter-hospital variation has not changed in the last four years.

There have been many studies of barriers to the uptake of thrombolysis(8–10). Eissa et al.(8) divided barriers into pre-admission and post-admission phases. Pre-admission barriers included poor patient response (not recognising symptoms of a stroke and not calling for help soon enough) and paramedic-related barriers (such as adding delays in getting the patient to an appropriate hospital in the fastest possible time). Hospital-based barriers include organisational problems (delay in recognising stroke patients, delays in pathway, poor infrastructure) and physician uncertainty or lack of experience leading to low use of thrombolysis. There has been significant discussion on how services may best be organised to optimise the effectiveness of thrombolysis(11).

Analysis of patient pathway data coupled with computer simulation has previously allowed investigation and improvement of thrombolysis use in individual hospitals - increasing both the number of patients treated and reducing door-to-needle times(12,13). These models have usually focused solely on the speed of the acute stroke pathway from arrival at hospital to treatment with thrombolysis(12). Interest in the use of simulation for improving the performance of the acute stroke pathway has reached an interest such that a common framework has been proposed(14).

Pathway modelling based on simulating process steps allows for good simulation of the speed of the stroke pathway, but cannot easily model differences in clinical decision making. We were interested in testing whether a model could dissect out the variation in thrombolysis rate that is dependent upon differences in patient populations (e.g. age or stroke severity) in different hospitals, and from the differences that are dependent on the culture of decision making at different hospitals (e.g. more cautious vs more aggressive clinical decision making). A variety of machine learning techniques now exist(15), which are able to make good predictions on pre-existing multidimensional data over a binary or categorical outcome variable (such as whether a patient receives thrombolysis or not). These have the potential to add modelling of clinical decision making to a model of the acute stroke pathway, with the aim of predicting what decision (to thrombolyse or not) would be made for the same patient in different hospitals. Models may also be trained on a reference standard set of hospitals (regarded as centres of clinical excellence) and use of thrombolysis for any patient predicted using that 'benchmark clinical

decision making model'. Machine learning has three key advantages for our approach: 1) it may use a variety of techniques (ranging from more traditional statistical regression models through to state-of-the-art Deep Learning Neural Networks) which may be combined into one outcome using a technique known as 'ensemble learning', 2) Machine Learning is highly scalable, with framework developed for dealing with very large numbers of patients each of which might have very many 'features' recorded. Models may, for example, in time be scaled to also make use of any imaging data available, 3) Machine Learning models may continually learn from new data without having to re-fit all previous and recent data together.

SSNAP is the prospective national stroke audit of in-patient stroke care in England, Wales and Northern Ireland, funded by the Healthcare Quality Improvement Partnership (HQIP) and hosted by the Royal College of Physicians of London and King's College London. Since inception in 2013, SSNAP now has over 300,000 case records from 127 acutely admitting hospitals. The Sentinel Stroke National Audit Programme (SSNAP) provides an opportunity to train models using data from all acute stroke hospitals in Engalnd, Wales and Northern Ireland, extracting learnings at both the generic and local level, with the ability to feed back, through the established quarterly audit process, to all hospitals.

Evidence explaining why this research is needed now: As detailed above there is considerable and persistent variation in the use and speed of thrombolysis, a time-critical treatment for stroke, which limits the disability benefit to individuals and the population from this cost-effective treatment. Advances in national audit data collection, and advances in scalable computational methods for pathway simulation and machine learning make this a timely project to introduce these advanced analytical tools into SSNAP's quarterly national stroke audit reports.

3. Aims and objectives

Simulation and machine learning

Our aim is to extend previous work on stroke thrombolysis pathway simulation in three significant ways: 1) to create a generic stroke thrombolysis pathway simulation model that could be readily applied to any hospital, 2) extend the analysis to include factors other than door-to-needle times, with special focus on differences in clinical decision making as analysed and modelled with machine learning techniques, and 3) use a modelling framework that is open source and fast enough to run routine analysis on all UK hospitals. We will also structure the model to make it suitable for extension to include mechanical thrombectomy, an emerging treatment for the most severe form of ischaemic stroke.

The combined simulation and machine learning would then be used in the quarterly national stroke audit, estimating the potential use of thrombolysis and the associated clinical benefit, by improving pathway speeds and processes, and by applying clinical decision making similar to the benchmark centres of clinical excellence. It is hoped that by applying machine learning model in an audit setting, though valuable alone, may also potentially lead to 'expert' advisory systems that may support clinical decision making (especially by less experienced clinicians).

Simulation and machine learning has been piloted using data from seven regional hospitals in the South West of England (see section on pilot work).

Qualitative research

A critical question of applying this type of advanced computational techniques is 'will the feedback change clinical practice for the better?' Qualitative research will be conducted with an overall objective to

determine individual and consensus physician perspectives and concerns towards the use of simulation and machine learning in reviewing and improving clinical practice in stroke thrombolysis.

Qualitative methods will be used to:

- Explore current attitudes and rationale for the use of thrombolysis for ischaemic stroke, in order to establish reasons for the variance in the use and speed of thrombolysis.
- Elicit physician perspectives on simulation and machine learning feedback, to understand how our results are best presented in a way that is useful and likely to have an impact on their practice.
- Identify potential routes for the implementation of machine learning feedback, to inform and improve future stroke management.
- Explore and anticipate possible unintended consequences of stroke pathway changes.

4. Research Plan / Methods

4.1 Design and theoretical/conceptual framework

The research consists of three key components, all relating to the use of thrombolysis in the acute stroke pathway.

1) Stroke pathway simulation.

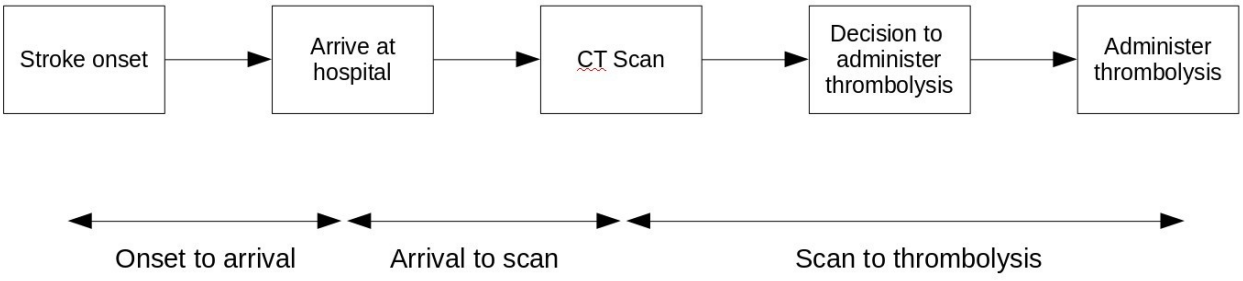
2) Patient level machine learning model on decision whether to administer thrombolysis (when there is time to administer thrombolysis).

3) Qualitative research exploring how physicians perceive the risks and benefits of using machine learning during audit to improve thrombolysis use for ischaemic stroke.

Pathway simulation model

(Project team members: Michael Allen, Kerry Pearn, Benjamin Bray, Martin James)

The pathway simulation model is coded in Python/NumPy and is based on sampling from distributions based on real-world data. Patients pass from one process stage to the next. The time spent in each stage is based on sampling from distributions derived from SSNAP data. Details of distributions used are given in Appendix 2.



For a patient to receive thrombolysis in the pathway model they must meet the following criteria: 1) stroke onset time known, 2) arrival at hospital within 4 hours of stroke onset, 3) have an ischaemic stroke and be judged to be eligible for thrombolysis, and 4) be within the licenced thrombolysis time window (4.5 hours and 3 hours onset-to-treatment time for patients aged under and over 80 respectively), when summing the process step times in the model. If a patient receives thrombolysis in the model then the probability of an additional good outcome (modified Rankin Scale [mRS] 0-1, no significant disability and able to carry out all usual activities) due to use of thrombolysis is calculated from the onset-to-treatment time and is based on the meta-analysis by Emberson *et al.(4)*.

If the pathway model is run without the machine monthlearning thrombolysis component (see next section), the likelihood of being given thrombolysis if scanned within 30 minutes is taken either from the hospital's own data on the proportion of patients who have time to receive thrombolysis (30 minutes licence window remaining after scan) and are given thrombolysis, or by using a published reference proportion (e.g. in the IST-3 trial 50% of stroke patients, if scanned with time left to treat, went on to receive thrombolysis(16)).

Model outputs: The primary outputs of the model are 1) an estimate of the proportion of patients receiving thrombolysis, and 2) expected clinical benefit achieved through use of thrombolysis (additional disability-free patients).

Model Validation: In order to validate the model, 3 years data (~225,000 patient records) will be split into two sets: Model parameters will be set using 75% of the data, and accuracy of the model compared with 25% test data not used for model training.

Scenario analysis: The model will be run for each hospital with key changes in the pathway, e.g. using upper quartile SSNAP data for determining stroke onset time, arrival-to-scan time, scan-to-treatment time, and the proportion of patients (with time left to treat) with decision to thrombolyse.

Pilot work: Please see section on pilot work for an example of use of the simulation model.

Clinical decision model (machine learning)

(Project team members: Richard Everson, Michael Allen, Kerry Pearn, Zhivko ZHelevl, Benjamin Bray, Martin James)

The clinical decision model aims to replicate the decision whether to give thrombolysis for any given patient at any given hospital. If patient features (characteristics) are kept unchanged, but the admission hospital is changed, the model should predict different expected decisions for the same patients in different hospitals. Differences in decisions between hospitals may be compared by passing the same randomly selected sample of patients to all hospitals (as differences between observed thrombolysis use between different hospitals may be complicated by differences in patient characteristics between different hospitals).

The model may be trained using different benchmarks. For example the model may be trained using a subset of hospitals recognised for their clinical excellence in acute stroke care. Possible subsets include hospitals in London which were found, as a group, to have improved outcomes following stroke care reorganisation/centralisation(17), or subgroups identified within the national audit with other organisational characteristics of excellence e.g. high rates of direct admission to an acute stroke unit, high rates of early dysphagia screening, etc.).

This model is intended to make decisions based only on clinical presentation, assuming that there is sufficient time remaining in which to assess and give thrombolysis. Patients are included if they have

been scanned with 30 minutes remaining in the licence window to give thrombolysis. The model is coded in Python using available SciKitLearn, Tensorflow, and PyTorch machine learning libraries.

The model predicts whether an individual patient should receive thrombolysis or not from a set of 50 parameters defining the patient's characteristics, clinical well-being, and hospital attended (see section on pilot work for a list of features used in the pilot work) that would all be available to the stroke clinician at the time of their thrombolysis use decision-making. The models are supervised learning models based on a training set of data with known use of thrombolysis. The machine learning models to be used are:

- Random Forests
- Support Vector Machines (SVM): linear and rbf
- Neural network (including basic freed-forward neural networks, and more advanced PyTorch and/ or Tensoflow neural networks).
- Logistic regression
- K nearest neighbours
- Gaussian process models
- Novel decision-tree methods (based on application of current work ongoing at the University of Exeter).

In addition to single type machine learning models, ensemble models will be built. These take the output from multiple different machine learning models and have been shown to be able to produce better accuracy than any single method alone(18).

Model outputs: The model outputs for each patient record entered whether thrombolysis would be given (along with a measure of probability of the decision).

Model Validation: In order to optimise and validate the model, data 3 years data (~225,000 patient records) will be split into three sets (randomly selected from stratified data to ensure all sets have similar over thrombolysis use). One set (25%) of the data will be held back for final testing after model selection and optimisation. The remaining 75% will be used for training and testing for model selection and optimisation using stratified k-fold validation (where the group is iteratively split, e.g. into ten 90% training and 10% test sets, so that all samples are part of a test set once and only once). The primary measure of performance will be ROC area under curve, with other outcomes reported (sensitivity, specificity, overall accuracy, F1 measurements).

Model scenarios: The aim of model scenarios is to ask 'what if?' questions of the model, to test the expected effect of hypothetical changes to the system.

A reference set of patients may be passed to each of the models that are trained on decisions made for patients from a single hospital, and thrombolysis use can be predicted for each hospital on this common reference set of patients. This will help identify hospitals that appear to have unusual thrombolysis use decisions (either significantly higher or lower than average, or significantly different to a benchmark group) independent of differences in patient populations attending each unit.

Where clinical decision making appears to significantly differ from benchmark hospitals, a cohort of patients from a single hospital (non-elite) may be passed to a model trained on patients from a benchmark set of hospitals (elite). That way, the use of thrombolysis within the non-elite centre (the recorded thrombolysis use) can be compared with the potential decision-making as would have

happened for that patient if they attended an elite centre (modelled thrombolysis use). To aid audit, a small group of patients will be identified for each hospital where modelled (based on the model trained using the benchmark set of hospitals) and actual thrombolysis use differ.

Our pilot studies give a strong indication of the robustness of the machine learning methods. Nevertheless if these initial results are not borne out over particular time epochs or at particular hospitals we will investigate the reasons, for example, if there is a difference in practice between pilot hospitals. This will give insight into the practice of the stroke treatment pathway and we will will construct alternative models to model these data. As an example, if accuracy is lower than anticipated, the results of individual machine learning models may be compared. If models differ from each other then the most likely issue is that the models are each too weak, in a random fashion, to attain high accuracy. In this case increasing the number of models used, and combining results (an 'ensemble of weak learners') offers a popular approach to improving accuracy. If accuracy is low but different models agree on the decision then this points to a systematic difference between model and data (for example one clinician in any one centre always making a different type of decision than other clinicians in that centre), and further investigation should focus on what additional data should be collected to improve accuracy (e.g. collecting data at clinician level in this hypothetical example).

The machine learning model may be used independently, but may also be combined with the pathway simulation mode. The combined model allows for investigation of the potential benefits of improving pathway processes and applying clinical decision making aligned with centres of clinical expertise. The combination may therefore provide a useful and realistic target use of thrombolysis given a hospitals own patient group characteristics.

Pilot work: We have performed extensive pilot work for project (for both simulation and machine learning aspects), and have included a separate section below on that work.

Qualitative research

(Project team members: Julia Frost, Ken Stein, Kristin Liabo)

Focus groups and semi-structured interviews will be conducted by an experienced qualitative researcher(20). We will recruit physicians via local, regional and national networks (clinical networks and the national specialist society, the British Association of Stroke Phycisians) and use maximum variance sampling to ensure inclusion of a range of relevant models of delivery and physician experiences such as: existing models of delivery, centres of excellence, type of hospital (regional centre or district hospital), any physician specialism (generalist, emergency care or stroke physician), and years in practice.

Three focus groups will be conducted in regional stroke centres in order to determine different clinician approaches and attitudes to the management of ischaemic stroke and thrombolysis practice(21). These groups will enable us to identify and pilot a range of visual displays and other methods of feedback from both pathway modelling and machine learning for use in individual interviews. We anticipate that these will involve: 1) national data, 2) regional data and 3) individual case data (or patient ‘vignettes’), to enable us to elicit perspectives and views about how best to present the feedback derived from machine learning.

30-40 interviews (face-to-face or telephone) will be undertaken with participant physicians, both career and training grades. Interviews will use a topic guide, based upon both the literature and expert opinion, and will ascertain which factors inform and influence clinical decision making and beliefs about the appropriate use of thrombolysis, or not. The second part of the interview will involve the introduction of

the data displays identified from the focus groups (and which can be sent ahead of any telephone interviews), and will identify which forms of data visualisation can best inform clinical practice. Patient and Public Involvement (PPI) representatives have enthusiastically endorsed the use of machine learning and qualitative methods and, reflecting earlier research(22,23) have suggested that our study materials must clearly emphasise why thrombolysis may, or may not be, of benefit to patients. All interviews will be audio recorded, transcribed verbatim and anonymised.

4.2 Sampling

SSNAP has near-complete coverage of all acute stroke admissions in the UK (outside Scotland). All hospitals admitting acute stroke participate in the audit, and year-on-year comparison with Hospital Episode Statistics confirms estimated case ascertainment of 95% of coded cases of acute stroke.

4.3 Setting/context

The model will use data from all English units registered as acutely admitting stroke units in SSNAP. Qualitative interviews will be held with stroke clinicians from acute stroke units in England.

4.4 Data collection and strorage

All patient-related data comes from SSNAP and is collected as part of routine care. We will access data through a single source managed by HQIP. Anonymised data will be handled in accordance with University of Exeter data protection policies. Qualitative research will be conducted in accordance with the General Data Protection Regulation and all relevant University Policies. See section 9 for details on ethics approvals for SSNAP and qualitative work.

4.5 Data analysis

Pathway simulation and machine learning

See Pilot Work and planned extensions for details of data analysis for ptahway modelling and machine learning.

Qualitative research

A thematic analysis of interviews will be conducted(24). The analysis will be iterative, moving between data collection and analysis to test emerging theories. This work will build upon the already identified barriers and facilitators to the use of thrombolysis, and will focus on the implementation of feedback from machine learning to optimise thrombolysis for ischaemic stroke management. We anticipate that this might involve the identification of examples of best practice that could inform the development of a future intervention to support quality improvement activities all along the pathway(25). Another possible output could be the development of a typology concerning the type of visualisation that might work best in a given scenario, e.g. whether they are organisational, clinician or patient factors.

A workshop will be conducted three months prior to project end, and up to 30 stakeholders will be invited to participate, which will include people who have had a stroke, carers, health professionals (physicians and members of the wider stroke team), NHS managers. The workshop will follow a structured format where participants engage in focused discussions, interspersed with brief presentations by the research team. We will present early findings from the various aspects of the research, including both the

simulation and machine learning, and the focus groups and interviews. Our PPI collaborators will also inform workshop participants about their contribution to the overall research project. Contingent on the nature of preliminary findings, activities will initially be in separate groups of professionals, patients, and others, followed by mixed groups of people from different backgrounds. This process and the multiple perspectives will be recorded in several ways, 1) by note-takers within sessions (JF, KL), 2) the researchers' participant observation notes made immediately after the stakeholder workshop and 3) participants' flipchart notes and summaries made during certain sessions. With consent, discussions will be audio-recorded, although we do not anticipate transcribing the whole event, rather recording will provide an aide memoire of the breadth of discussions as opposed to the attribution of data at an individual level. Thematic analysis of this data will augment and triangulate preliminary findings, to inform the development of an intervention to support quality improvement in thrombolysis practice. Previous experience with this method suggests that it will contribute concerns and issues that might otherwise be by those conducting the research and also offer additional interpretations and suggestions for implementation(26,27).

Following feedback from the review board we aim to use the qualitative work to also explore views on what unintended consequences may come about from changing the acute stroke pathway, and how might such adverse effects be detected and mitigated. We will produce a summary of these points in the form of a Failure Mode Effects Analysis (FMEA) as used in engineering when trying to anticipate what may go wrong with a product.

5. Pilot work

Pathway simulation and machine learning methods, has been piloted using SSNAP data from seven acute stroke units.

5.1 Data

SSNAP data was obtained from 7 hospitals in England, for patients with a confirmed stroke over a period of two years (2013-2014) for each hospital. These data were anonymised secondary data, collected during routine care. No patient identifiable information was obtained. For the pathway simulation model, the dataset contained 7,864 patient records with complete data for 12 parameters regarding their characteristics and time stamped pathway location. These data represent out-of-hospital onset of stroke (which account for 94% of all cases of acute stroke in the SSNAP data used). For machine learning, only those patients with a completed National Institutes of Health Stroke Scale (NIHSS) and who had at least 30 minutes left to give thrombolysis were used (1,862 patients).

5.2 Pathway simulation

Hospital	1	2	3	4	5	6	7
Actual thrombolysis use	13.7%	8.0%	8.5%	7.2%	7.7%	14.3%	9.5%
Aged 80+	50.2%	51.3%	41.3%	49.8%	45.8%	51.1%	48.9%
Onset time known[1]	67.8%	53.7%	53.3%	43.4%	44.6%	72.7%	56.2%
Known arrival within 4 hours of onset[2]	68.4%	69.8%	69.3%	67.7%	69.7%	70.5%	70.3%
Average arrival time after onset (min)[3]	96	87	95	100	82	93	87
% Patients scanned within 4 hours[3]	84.4%	78.3%	94.7%	97.9%	83.7%	84.9%	91.3%
Average arrival to scan (min)[4]	38.3	30.6	43.6	11.9	40.5	28.6	22.1
Proportion ischaemic stroke[5]	86.4%	88.5%	85.2%	85.8%	89.2%	85.7%	88.2%
Proportion ischaemic patients receiving thrombolysis[5]	55.7%	38.6%	39.2%	34.4%	44.5%	49.5%	34.7%
Average scan to treatment (min)	22	36	44	40	35	35	36

[1]The known onset time may be recorded as precise or best estimate.
[2]of those with known time of onset
[3]for those arriving within 4 hours of known onset
[4]for those arriving within 4 hours of known onset and having a scan within 4 hours of arrival
[5]for those scanned with 30 minutes left to administer thrombolysis

Table 1. Key characteristics for the seven hospital pathways modelled. The number of good outcomes (modified Rankin Scale 0-1, no significant disability) without any use of thrombolysis was estimated at being 238-260 per 1,000 stroke patients admitted depending on the hospital (the differences being due to differences in age profile of patient populations).

Table 1 shows the key characteristics for the seven hospital pathways modelled. The model was validated by comparing modelled (predicted) use of thrombolysis with actual use. Predicted use was based on modelling a one year period, with replicates of 100 runs (each with different random number seeds to sample a different value from each distribution for each of the 100 runs with different random seeds) in order to determine expected year-to-year variation. The model showed excellent agreement (R-square 0.981) between actual and predicted values though the model slightly under-predicted actual thrombolysis use by an average of 0.84% (figure 2).

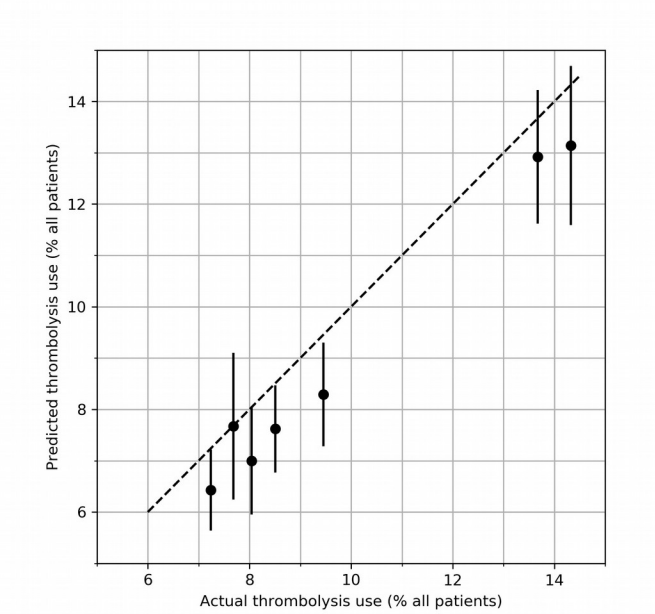


Figure 2. Validation of the pathway simulation model, comparing actual to modelled (predicted) thrombolysis use at seven hospital. Points show mean predicted thrombolysis use for all confirmed stroke patients arriving at hospital, with bars showing 5th and 95th percentiles from 100 runs, with each run modelling one year.

The model was run with various 'what-if?' scenarios for each of the seven hospitals (Table 2):

1. Base case: Model based on parameters derived from current hospital-specific performance
2. Scenario A: Door-to-needle time fixed at 30 minutes (by fixing arrival-to-scan time and scan-to-thrombolysis both at 15 minutes (with no variation in either time)
3. Scenario B: Judged to be eligible for thrombolysis fixed at 60% of ischaemic strokes. An analysis of ECASS-3/IST-3 results concluded that 591 out of 992 (59.6%) of ischaemic stroke patients arriving within 4 hours of stroke onset were ultimately considered suitable for thrombolysis(16).
4. Scenario C: Onset time known fixed at 77% (national SSNAP upper quartile for year 2015/16(2))
5. Combination of all of the above

In order to achieve the greatest improvement in thrombolysis use in each of the seven hospitals, for three hospitals (hospitals 1, 2 and 6) it would be best to improve the speed of the pathway, for two hospitals (hospitals 4 and 5) it would be best to improve determination of stroke onset time, and for two (hospitals 3 and 7) it would be best to judge more patients as eligible for thrombolysis for those scanned with time left to treat. If a priority is to maximise clinical outcome then for five hospitals (hospitals 1, 2, 3, 5 and 6) it would be best to improve the speed of the pathway, for one hospital (hospital 4) it would be best to improve the determination of stroke onset time and for one (hospital 7) it would be best to judge more patients as eligible for thrombolysis for those scanned with time left to treat. Combining all changes in the model could produce thrombolysis rates up to 22-26%, and 23-26 additional non-disabled outcomes per 1,000 stroke patients admitted.

	Hospital	Base	A	B	C	ABC
Thrombolysis use (%)	1	12.7 (0.2)	17.4 (0.3)	13.7 (0.3)	14.6 (0.3)	21.1 (0.3)
	2	6.9 (0.2)	10.3 (0.3)	11.0 (0.3)	9.9 (0.2)	23.0 (0.3)
	3	7.6 (0.2)	10.1 (0.2)	12.2 (0.2)	11.1 (0.2)	22.2 (0.3)
	4	6.4 (0.2)	6.5 (0.2)	11.1 (0.3)	11.5 (0.2)	20.6 (0.3)
	5	7.4 (0.3)	10.2 (0.3)	10.2 (0.3)	13.1 (0.4)	23.8 (0.5)
	6	13.5 (0.3)	17.2 (0.4)	16.4 (0.4)	14.0 (0.4)	22.4 (0.4)
	7	8.2 (0.2)	9.6 (0.3)	14.3 (0.2)	11.2 (0.2)	22.8 (0.3)
Additional good outcomes per 1,000 admissions	1	11.1 (0.2)	16.9 (0.3)	12.0 (0.2)	12.7 (0.3)	20.6 (0.3)
	2	5.9 (0.2)	10.3 (0.3)	9.5 (0.3)	8.6 (0.2)	22.8 (0.4)
	3	6.3 (0.2)	10.3 (0.2)	10.0 (0.2)	9.1 (0.2)	22.6 (0.3)
	4	5.5 (0.2)	6.3 (0.2)	9.6 (0.2)	10.0(0.2)	19.9 (0.3)
	5	6.5 (0.3)	10.5 (0.4)	8.9 (0.3)	11.4 (0.4)	24.4 (0.5)
	6	11.5 (0.3)	16.8 (0.4)	14.1 (0.4)	11.8 (0.3)	21.8 (0.4)
	7	7.3 (0.2)	9.7 (0.3)	12.8 (0.2)	10.0 (0.2)	23.0 (0.3)

Table 2. Predicted thrombolysis use and clinical benefit across all modelled hospitals (1 to 7). Data shows: (Base) Model based on parameters derived from current performance; (A) Arrival-to-scan and scan-to-thrombolysis both fixed at 15 min (with no variation in either time); (B) Judged to be eligible for thrombolysis fixed at 60%; (C) Onset time known fixed at 77%; Combinations of the above. Results show mean and ±95% confidence limits (1,000 runs).

In the case of hospital 5, arrival-to-scan times could be slowed by an average of 30 minutes and clinical outcomes would still be greater if that hospital achieved a proportion of known stroke onset time equal to the national average.

5.3 Clinical decision (machine learning) model

Machine learning models were trained and tested on the subset of patients who have 30 minutes left to treat after scanning. Patient features used in the model are given in Appendix 3. Across the seven hospitals an average of 40% of these patients actually received thrombolysis, though use ranged from 31% to 52% in different hospitals.

Table 3 shows the performance of the various machine learning models. The models had 80-82% accuracy, and 88-89% ROC area under the curve. The Random Forest machine learning model was chosen to use from this point onwards.

	accuracy	sensitivity	specificity	ROC area
Logistic regression	0.807 (0.010)	0.788 (0.015)	0.819 (0.012)	0.882 (0.005)
Random Forest	0.819 (0.010)	0.792 (0.017)	0.837 (0.011)	0.889 (0.007)
SVM (linear)	0.807 (0.008)	0.820 (0.012)	0.798 (0.012)	0.880 (0.005)
SVM (rbf)	0.813 (0.006)	0.820 (0.013)	0.808 (0.008)	0.880 (0.006)
Neural Network	0.807 (0.010)	0.794 (0.017)	0.816 (0.012)	0.882 (0.005)

Table 3. *Accuracy, sensitivity, specificity, and ROC (Receiver-Operator Curve) area of five different machine learning models. Results show mean and standard error based on a 10-fold stratified validation/test split.*

A machine learning model may be trained on a subset of patients to investigate how the difference in thrombolysis use between hospitals may be proportionally attributed to either the hospital or the local patient population. Table 4 shows the predicted use of thrombolysis in a set of patients that attend one hospital, based on decisions made from training at another hospital. Taking hospital 7 as an example, between 31% to 45% of the patients that currently attend hospital 7 (with time left to receive

thrombolysis) might receive thrombolysis depending on which hospital decision making is used to train the model. Patient cohort also affects the predicted thrombolysis uses. Taking hospital 7 as an example again, if the model is trained on decisions made for patients attending hospital 7, and different hospital patient groups are then analysed in the model then thrombolysis use is to be between 23% and 50% depending on the hospital patient group analysed.

Actual thrombolysis use by hospital

1	2	3	4	5	6	7	All
52%	35%	48%	33%	49%	44%	31%	40%

Predicted thrombolysis use

		Hospital patients actually attended							
		1	2	3	4	5	6	7	All
Hospital used to train model	1	52%	42%	58%	50%	67%	57%	45%	51%
	2	48%	35%	55%	36%	46%	37%	29%	40%
	3	53%	38%	48%	46%	58%	41%	34%	44%
	4	40%	28%	48%	33%	52%	29%	26%	35%
	5	50%	36%	50%	40%	49%	45%	37%	43%
	6	49%	32%	55%	44%	59%	44%	39%	44%
	7	42%	23%	42%	31%	50%	36%	31%	35%

Table 4. Predicted thrombolysis use (for patients with patients scanned with time left to receive thrombolysis) if the decision to give thrombolysis is based on decisions made by a Random Forest model trained at different hospitals. The columns therefore represent the likely difference in thrombolysis use due to differences in decision making.

5.4 Combining pathway simulation and machine learning

The output from machine learning may be incorporated into the stroke pathway model by using the machine learning model to make the decision in the pathway model about whether a patient is 'judged to be eligible for thrombolysis (for patients scanned with 30 minutes left to administer thrombolysis)'. This should tailor the clinical decision to the local population, without being affected by any particular hospital's predisposition to use thrombolysis. The 'judged to be eligible for thrombolysis' parameter in the pathway model may take its value from a machine learning model trained using a reference set of hospitals. The clinical decision making from these reference hospitals may be used to predict which of the patients from the hospital under study are eligible for thrombolysis.

Table 5 compares base case hospital performance (predicted thrombolysis use and clinical benefit) with the performance obtainable by a new realistic 'alternative' practice which is in part informed by the Random Forest machine learning model: (1) the proportion of patients with a known stroke onset time is set at the national median (67%) unless a hospital is already higher, (2) the door-to-needle time is set to 40 minutes for 90% of patients (20 minutes arrival-to-scan, and 20 minutes scan-to-needle) with the other 10% of patients not receiving a scan within 4 hours of arrival, and (3) the clinical decision to administer thrombolysis for those patients scanned with 30 minutes left to treat is set by the machine learning model trained from a reference hospital (this example uses the hospital that has the highest use of thrombolysis for those patients scanned with time to treat). Resulting thrombolysis targets vary from 16-25% depending on the hospital (base case 6 to 13%).

	Thrombolysis use (%)		Clinical benefit: Additional good outcomes per 1,000 admissions	
Hospital	Current	Alternative	Current	Alternative
1	13.0 (0.3)	18.8 (0.3)	11.4 (0.3)	17.6 (0.3)
2	6.8 (0.2)	15.6 (0.3)	5.9 (0.2)	14.9 (0.3)
3	7.9 (0.2)	21.7 (0.3)	6.5 (0.1)	21.2 (0.3)
4	6.4 (0.2)	17.1 (0.3)	5.5 (0.2)	16.0 (0.3)
5	7.6 (0.3)	25.8 (0.5)	6.7 (0.3)	25.7 (0.5)
6	13.1 (0.3)	23.2 (0.4)	11.3 (0.3)	21.8 (0.4)
7	8.2 (0.2)	16.8 (0.3)	7.2 (0.2)	16.3 (0.3)

Table 5. Combining pathway simulation and machine learning. Predicted thrombolysis use and clinical benefit (additional good outcomes per 1,000 admitted patients) across all modelled hospitals (1 to 7) from the pathway simulation. Data shows: (Base) Model based on parameters derived from current performance; (Alternative) New realistic practice, fixing the proportion of known stroke onset times to the national SSNAP average (67% median) unless the hospital currently performs higher, fixing arrival-to-scan and scan-to-needle to 20 minutes each (with 10% of patients not scanned within 4 hours), and fixing the proportion of treatable patients (scanned with 30 minutes left to treat) according to the output of the machine learning model based on the hospital with the maximum predicted proportion given thrombolysis. Data shows mean and 95% confidence intervals.

5.5 Planned extension to pilot work

The pilot pathway simulation and machine learning work will be extended in the following ways:

- Use data for all acute stroke units in England
- Add analysis of time epochs to pathway simulation model (e.g. day/night/weekday/weekend) to test targeting of potential pathway improvements by time epoch.
- Optimise performance of current machine learning models (e.g. by refining selection of data used, testing of polynomial functions in inputs, testing of use of principal component analysis, optimising model meta-parameters).
- Apply additional machine learning techniques (e.g. k-nearest neighbours, Gaussian processes, novel Decision Tree methods, ‘deep-learning’ neural networks from PyTorch and Tensorflow).
- Apply ensemble techniques to combine multiple machine learning techniques to produce a single outcome.
- Incorporate confidence of decision into output.
- Produce machine learning code that will either work on all SSNAP data or on smaller-batch data to allow continual learning/update of the model with each run without having to process the whole data set each time.
- Structure simulation and machine learning models in such a way that they may extended in the future to include mechanical thrombectomy.
- Identify one or more sets of hospitals to use as benchmark hospitals for training the model. We are currently planning to use subgroups of hospitals identified by a range of other markers of clinical quality (e.g. .those with the highest rates of direct admission to an acute stroke unit within 4 hours), but we will also explore subgroups of hospitals of similar size and patient demographics to allow comparisons with a ‘similar 10’.

- Identify a reference group of patients (either through sequential or random sampling). These will be used as a final test and validation of the model
- Identify a second reference group of patients through random sampling (with or without stratification) to act as a representative sample that may be used to estimate the differences in use of thrombolysis between different hospitals given the same population group.
- Identify a subset (30 patients) of the representative patient group to give to small groups of stroke clinicians and ask them (independently) to make a decision whether they would or not give thrombolysis to these patients from the SSNAP data provided. We will compare cross-physician agreement on treatment decisions. We will also ask what additional information would have given greater confidence in the decision made.
- Produce a variety of visualisations of outputs from the pathway simulation and machine learning models for use in the qualitative research outlined above. Visualisations will be at 1) a national level, and 2) individual trust level.
- Run at least two pilots applying code as part of the national stroke audit (the first pilot will be used to test and refine the code for 'production' use, and the second pilot will generate output that will be given to all stroke units).
- Following feedback from a PPI meeting we also plan to perform some exploratory work at using machine learning method to predict outcomes (both benefit and risk of haemorrhage) at patient-level (the main model described performs clinical benefit analysis at a net population level). Decisions, if the tool were applied in a live decision-aid setting, could allow adjustment for patients acceptability of risk. We anticipate this work laying ground for further separately-funded work.

6. Dissemination, Outputs and anticipated Impact

6.1 What do you intend to produce from your research?

We have four production aims:

1) To produce code that will be routinely used by the national stroke audit SSNAP as part of their quarterly outputs to participating hospitals and commissioning groups, and in national reports. The code will have a structure for potential future extension to mechanical thrombectomy (an emerging alternative to thrombolysis for the most severe ischaemic strokes).

2) To publish the code in a public Open Source code repository (e.g. GutHub or GitLab).

3) To produce papers (in addition to the NIHR monologue)on at least:

- Application of machine learning to audit of thrombolysis use (technical machine learning publication)
- Application of combined simulation and machine learning to stroke thrombolysis audit (suitable for general/clinical readership)
- Qualitative publication of facilitators and barriers to use of computer simulation and machine learning in national audits.

4) Presentation of above paper themes at the UK stroke forum and an international stroke conference.

6.2 How will you inform and engage patients, NHS and the wider population about your work?

Working through SSNAP gives us a means of engaging with all stroke units as the models are implemented. We will also engage with clinicians through attendance and presentation at the national stroke forum. We also have support from the Stroke Association (see letter of support attached in appendices) to plan and implement wider engagement. With PPI involvement in the project we will will produce dissemination material suitable for public and patients.

6.3 How will your outputs enter our health and care system or society as a whole?

Although our principal aims relate primarily to increasing the effectiveness and impact of the national stroke audit SSNAP in increasing the uptake of treatments for acute stroke and reducing disability, we consider our work to have potential applications and transferability into other clinical areas, particularly those relating to other time-sensitive treatments and where considerable clinical variation persists. Our qualitative outputs may similarly transfer into the quality improvement field in clarifying methods to improve the reach and impact of comparative data in other national audits e.g. the Renal Registry, the National Diabetes In-patient Audit etc.

6.4 What further funding or support will be required if this research is successful (e.g. from NIHR, other Government departments, charity or industry)?

None to apply what we have done, as we will make our code able to run routinely. There are opportunities for further development. For example if machine learning proves accurate in predicting practice audit, a next step could be to format the models into a form that they could be used for clinical guidance in routine care (including the potential to predict outcome likelihoods given individual patient characteristics). We would also expect the model in future to be developed to include use of thrombectomy in addition to thrombolysis.

6.5 What are the possible barriers for further research, development, adoption and implementation?

We recognise that there is mistrust of methods of artificial intelligence as applied to complex clinical situations, and the qualitative component of our proposal seeks to directly address this issue. Adoption and implementation will be hampered without a thorough understanding of these barriers from our research, which may identify other, as yet unforseen, obstacles to wider acceptance. We are helped in this by the established credibility of SSNAP as a national comparative audit, and our proposal to pilot our dissemination methods leaves plenty of scope to explore these issues further, in order to mitigate them.

6.6 What do you think the impact of your research will be and for whom?

This work is intended to benefit stroke patients through improved stroke pathways and improved decision making regarding the use of thrombolysis. We believe there is a wider benefit of helping to establish simulation and machine learning in healthcare audit and practice.

7. Project / research timetable

Pre-work: Data access application to HQIP & access data from SSNAP. Ethics application for qualitative work through our local research ethics committee (REC) and via the Integrated Research Application System (IRAS).

Months 0-9: Primary focus is on development of simulation and machine learning models. Add epochs (day/night/weekday/weekend) to pathway model. Optimise current machine learning models for on national dataset. Apply additional machine learning methods and develop ensemble model. Identify a subset of hospitals to be used as a benchmark for thrombolysis decisions. Identify reference group of representative patients to use to compare decisions in different hospitals. Identify a smaller subset of patients to ask three clinicians to judge whether they would likely give thrombolysis or not. Produce a variety of visualisations of outputs from the pathway simulation and machine learning models (this will not require models to be finalised – development of models should refine accuracy rather than change the type of output produced). Preliminary visualisations will be produced in the first four months based on pilot regional work. This will allow an early start to qualitative interviews (which depend on example analysis); national level visualisations should begin to be available within the first nine months of the project.

Months 10-18: Qualitative phase of project to conduct 30-40 interviews with stroke clinicians on outputs of modelling. Continue to refine and expand machine learning models. Visualisations will be refined during this phase following feedback from clinicians. Provide code to SSNAP at 12 and 18 months (code will work on a standard CSV export from SSNAP database).

Months 19-24: Qualitative stakeholder workshop, writing of papers, refining code and making it of publication quality (e.g. well commented for other people to follow and amend).

(Patient involvement continues through project through membership of steering and project groups.

(PPI continues through project through membership of steering and project groups).

MILESTONES:

1) **End month 4:** Visualisations and summary of output from pilot regional work will be provided for beginning qualitative interviews. Qualitative work to being after these visualisations produced.

2) **End month 6**: Qualitative work to have begun (initially based on outputs from regional pilot work).

3) **End Month 9**: First outputs from national model will be generated with prototype visualisation of results that may be used for qualitative work. This will not be the final model, but should be advanced enough to form the basis of results that can be shared with clinicians, and a PPI group, through the qualitative work of the project.

4) **End of months 12 and 18**: provide code to SSNAP that will perform analysis and produce reports/visualations. This code will run on CSV file formats from SSNAP (providing an easy method to test and use code as a stand-alone module).

5) **End of month 18**: 1:1 qualitative interviews and focus groups complete.

6) **End of month 21**: Qualitative stakeholder workshop complete.

7) **End of month 24**: Papers to be complete (see dissemination), model code to be published (GitHub).

8. Project management

There will be an independent advisory board which will meet prior to project start, six months into project, and four months from the end. The membership of this advisory board is:

- Dr Thomas Monks (Operations Research, Southampton, Chair)
- Prof Anthony Rudd (National Clinical Director for Stroke)
- Prof Gary Ford (CEO Oxford AHSN, Stroke Physician, Prof Clinical Pharmacology, Oxford)
- Prof Nicky Britten (Professor of Applied Health Care Research, Exeter)

There will be a steering committee composed of Prof Ken Stein, Dr Martin James, Dr Benjamin Bray, Prof Richard Everson, two lay PPI members (separate from the project team) and one independent senior stroke physician/academic (to be approached). The steering committee will ensure that the project delivers on the stated aims and is kept in close alignment and contact with the National Stroke Audit team. The steering committee will meet every six months.

The project team will meet quarterly, and will consist of all project team members, including two patients and members. One carer member is a named collaborator to this application (PT).

The project team will meet monthly, and will consist of all project team members, including two patients and members. One carer member is a named collaborator to this application (PT).

9. Ethics / Regulatory Approvals

9.1 Access to SSNAP data for simulation and machine learning

All patient data will be from a single source: The Sentinel Stroke Audit Programme (SSNAP). No identifiable patient information will be requested or used. Explicit consent for the use of patient identifiable information is not required (although patients can choose to ‘opt-out’ from SSNAP at individual sites) as the audit has received exemption via section 251 of the NHS Act 2006, and so separate ethical approval for this work is not required. The section 251 approval comes from the Ethics and Confidentiality Committee of the National Information Governance Board (now superseded by the NHS Health Research Authority Confidentiality Advisory Group). The data controller is HQIP, and data access is managed through the the HQIP Data Access Request process, which attracts a £10,000 fee included in the application. The HQIP data access request group meets monthly, with outcomes communicated within 2 weeks of meetings. We plan to submit the HQIP request for access so that it is granted before planned project start (Feb 2018).

9.2 Qualitative research

For the qualitative work, we will seek the advice of our local research ethics committee (REC) on ethical matters as appropriate, and ethical approval will be sought via the Integrated Research Application System (IRAS).

Qualitative research will be conducted in accordance with the Data Protection Act and University Policy.

10. Patient and Public Involvement

This application was discussed with five members of the Peninsula Public Involvement Group. We This application was discussed with five members of the Peninsula Public Involvement Group. We discussed this with this group because they have experiences as in-patients or carers, and are interested in improving hospital care. They have also previously attended a workshop on simulation modelling in health services research and planning.

At the meeting they reviewed the Plain English Summary and gave feedback on its readability. They also discussed, with modellers Mike Allen and Kerry Pearn, the appropriateness and relevance of the proposed study and the research plan. In addition, they reviewed the qualitative research component in discussion with qualitative lead Julia Frost. Specific impact from these discussions were the following points, which have all been incorporated into the application:

- To frame the output of this study as a potential ‘decision-making tool’ for physicians
- To consider how, in the future, this decision-making tool might take patients’ views on risk/benefit balance into account
- To include some pilot modelling on outcomes at patient level
- To take different data displays to the qualitative interviews, to find out which forms of data might be most helpful
- To invite the Stroke Association to be a collaborator to the study

Overall the public advisors were positive to the study and see it as vital in improving understanding of when administration of thrombolysis is appropriate and when it’s not.

After these discussions the Plain English Summary was amended and the new version was reviewed by two people, with direct experience of stroke as next of kin to a patient, who were unable to attend the meeting. Finally, this section and the involvement plans described below were reviewed by members of the Peninsula Public Involvement Group.

PPI involvement throughout project

Support for involvement: This study is supported by the PenCLAHRC involvement team at the University of Exeter Medical School. The team has a track record of supporting people with complex needs to be research advisors. All involved patents and carers will have their travel fully reimbursed and their time recognised with a thank-you payment. Thank-you payments will be higher for patients on the steering committee, in recognition of their longer travel time. We have budgeted for an introductory training course for people new to involvement. Co-applicant Kristin Liabo will provide tailored support in advance of, during and after meetings.

Governance: Penny Thompson cares for her husband who has several health problems after a stroke. She is a collaborator on the study. Her husband has decided that he will contribute knowledge when he feels it is appropriate. PT also cared for her father after he had a stroke. As collaborator PT will attend quarterly project team meetings. We will recruit another stroke survivor to attend with her. Two patient or carer members will be invited to sit on the study steering committee. They will be asked through a national organisation so we have input from outside the South West.

Involvement group: We will set up a group of stroke patients and carer advisors to the study. The group will consist of 6-8 members and will meet three times during to discuss: research findings (meeting 1),

how the decision-making tool might take patients' views on risk/benefit balance into account (meeting 2), planning for the stakeholder engagement event described in the qualitative research section of this proposal (meeting 3). Patients and carers who are collaborators, and those who sit on the study steering committee, will be invited to join this group. If they prefer, they can input to the group remotely.

A workshop will be organised with up to 30 stakeholders, including people who have had a stroke, carers, health professionals and NHS managers. The workshop will follow a structured format where participants are presented with early findings from the research, including the pathway simulation and machine learning models, the focus groups and the interviews. Our patient and carer collaborators will also present on their contribution to the study. Contingent on the nature of preliminary findings, activities will first be in separate stakeholder groups, followed by mixed groups of people from different backgrounds. This process and the multiple perspectives will be recorded in several ways: 1) by note-takers within sessions (JF, KL); 2) the researchers' participant observation notes made immediately after the stakeholder workshop and 3) participants' flipchart notes and summaries made during certain sessions. With consent, discussions will be audio-recorded, although we do not anticipate transcribing the whole event, rather recording will provide an aide memoir of the breadth of discussions as opposed to the attribution of data at an individual level. Thematic analysis of this data will augment and triangulate preliminary findings, to inform the development of an intervention to support quality improvement in thrombolysis practice. This method helps contribute to the study with stakeholders' concerns and offer additional interpretations and suggestions for implementation based on the study's findings.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. The Lancet. 2014;383(9913):245–255.

2. Sentinel Stroke Audit Programme (SSNAP). Apr2015Mar2016-AnnualResultsPortfolio. 2016.

3. Newton JN, Briggs ADM, Murray CJL, Dicker D, Foreman KJ, Wang H, 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. The Lancet. 2015;386(10010):2257–2274.

4. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, 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. The Lancet. 2014;384(9958):1929–1935.

5. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke thrombolysis: Save a minute, save a day. Stroke. 2014;45(4):1053–1058.

6. Saver JL. Time is brain - Quantified. Stroke. 2006;37(1):263–266.

7. Lyden P. Thrombolytic Therapy for Acute Stroke — Not a Moment to Lose. N Engl J Med. 2008;359(13):1393–1395.

8. Eissa A, Krass I, Bajorek BV. Barriers to the utilization of thrombolysis for acute ischaemic stroke. J Clin Pharm Ther. 2012;37(4):399–409.

9. Carter-Jones CR. Stroke thrombolysis: Barriers to implementation. Vol. 19. 2011. 53–57 p.

10. Engelter ST, Gostynski M, Papa S, Ajdacic-Gross V, Lyrer PA. Barriers to stroke thrombolysis in a geographically defined population. Cerebrovasc Dis. 2007;23(2–3):211–215.

11. Lahr MMH, Luijckx GJ, Vroomen PCAJ, Van Der Zee DJ, Buskens E. The chain of care enabling tPA treatment in acute ischemic stroke: A comprehensive review of organisational models. Vol. 260. 2013. 960–968 p.

12. Monks T, Pitt M, Stein K, James M. Maximizing the population benefit from thrombolysis in acute ischemic stroke: A modeling study of in-hospital delays. Stroke. 2012;43(10):2706–2711.

13. Lahr M, van der Zee D-J, Luijckx G, Vroomen P, Buskens E. A simulation-based approach for improving utilization of thrombolysis in acute brain infarction. Med Care. 2013;51(12):1101–1105.

14. Monks T, Pitt M, Stein K, James M a. Hyperacute stroke care and NHS England's business plan. BMJ. 2014;348(May 2014):g3049.

15. Kotsiantis SB, Zaharakis I, Pintelas P. Supervised machine learning: A review of classification techniques. Informatica. 2007;31:249–268.

16. Bembenek J, Kobayashi A, Sandercock P, Czlonkowska A. How many patients might receive thrombolytic therapy in the light of the ECASS-3 and IST-3 data? Vol. 5. 2010. 430 p.

17. Morris S, Hunter RM, Ramsay AIG, Boaden R, McKevitt C, Perry C, 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(aug04 4):g4757–g4757.

18. Rokach L. Ensemble-based classifiers. Artif Intell Rev. 2010;

19. Markatou M, Tian H, Biswas S, Hripcsak G. Analysis of variance of cross-validation estimators of the generalization error. J Mach Learn Res. 2005;6:1127–1168.

20. Pope C, Mays N. Qualitative Research in Health Care. 2006.

21. Green J, Thorogood N. Qualitative Methods for Health Research. 2009.

22. Hangar HC, Fogarty B, Wilkinson TJ, Sainsbury R. Stoke patients' views on stroke outcomes: death versus disability. Clin Rehabil. 2000;14:417–424.

23. Flatharta TO, Khan A, Walsh T, O'Donnell M, O'Keefe ST. Advance preferences regarding thrombolysis in patients at risk for stroke: a cross-sectional study. QJM Mon J Assoc Physicians. 2015;

24. Miles MB, Huberman MA, Saldaña J. Qualitative Data Analysis. A Methods Sourcebook. Z Für Pers. 2014;28(4):485–487.

25. Healthcare Quality Improvement Partnership. Rising to the Challenge: The Fourth SSNAP Annual Report. 2017;

26. Raynor DKT, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines. Health Technol Assess. 2007;

27. Frost J, Garside R, Cooper C, Britten N. A qualitative synthesis of diabetes self-management strategies for long term medical outcomes and quality of life in the UK. BMC Health Serv Res. 2014;

11. Appendices

11.1 Hospital performance parameters used in the pathway simulation model

The parameters used in the thrombolysis pathway simulation model are shown in table A1.

Index	Parameter	Distribution	Range used (base case)
1	Allowed onset-to-treatment time for age up to 80 (mins)	Fixed	270
2	Allowed onset-to-treatment time for age 80 + (mins)	Fixed	180
3	Age 80+	Bernoulli	0.413-0.513
4	Arrivals per year	fixed	300-800
5	Onset time known	Bernoulli	0.434-0.727
6	Onset-to-arrival <4hrs	Bernoulli	0.677-0.705
7	Onset-to-arrival time (mins)	Log (ln) normal	Mean (ln): 4.411-4.609 StdDev (ln): 0.475-0.588
8	Arrival-to-scan <4hrs	Bernoulli	0.78-0.97
9	Arrival-to-scan time (mins)	Log (ln) normal	Mean (ln): 2.477-3.776 StdDev (ln): 0.750-1.271
10	Ischaemic stroke	Bernoulli	0.85-0.89
11	Eligible for thrombolysis	Bernoulli	0.344-0.571
12	Scan-to-thrombolysis (mins)	Log (ln) normal	Mean (ln): 2.970-3.791 StdDev (ln): 0.578-0.849

Table A1: parameters used in the stroke pathway simulation model.

Notes:

1. *The allowed onset-to-treatment time for patients aged up to 80 is 4.5 hours.*
2. *The allowed onset-to-treatment time for patients aged 80+ is 3 hours.*
3. *The proportion of patients aged 80+ varies between hospitals.*
4. *The number of arrivals is the number of confirmed stroke patients in SSNAP per year*
5. *'Onset time known' is binary yes/no. Known onset time may be recorded as precise or estimated in SSNAP. Those without a known onset time cannot be treated with thrombolysis in the model.*
6. *'Onset to arrival <4hrs' is the proportion of patients with known stroke onset that arrive within 4 hours of onset. Those arriving more than 4 hours after onset cannot be treated with thrombolysis in the model.*
7. *'Onset to arrival time' is a log-normal distribution. It is applied only to those patients arriving within 4 hours of known stroke onset.*
8. *'Arrival to scan time <4hrs' is the proportion of patients (those with known stroke onset time and arriving within 4 hours of onset) that receive a CT head scan within 4 hours of arrival.*
9. *'Arrival to scan time' is a log-normal distribution. It is applied only to those patients arriving within 4 hours of known stroke onset, and receiving a scan within 4 hours of arrival.*
10. *'Ischaemic stroke' is the proportion of patients with ischaemic (rather than haemorrhagic stroke). It is applied only to those patients arriving within 4 hours of known stroke onset, and receiving a scan within 4 hours of arrival.*
11. *'Eligible for thrombolysis' is the proportion of ischaemic stroke patients (arriving within 4 hours of known stroke onset, and scanned within 4 hours of arrival) who are considered clinically eligible for thrombolysis.*

This figure is obtained by examining the proportion of ischaemic stroke patients who are scanned with at least 30 minutes left to thrombolyse who are given thrombolysis.

12. *'Scan to thrombolysis' is a log-normal distribution. It is applied only to those patients arriving within 4 hours of known stroke onset, receiving a scan within 4 hours of arrival, and are ischaemic strokes considered eligible for thrombolysis.*

11.2 SSNAP features used in pilot machine learning

The following factors were used in the pilot study:

Thrombolysis given	Anticoag before stroke_1
Hosp_1	Anticoag before stroke_NK
Hosp_2	Stroke severity group_1. No stroke symtpoms
Hosp_3	Stroke severity group_2. Minor
Hosp_4	Stroke severity group_3. Moderate
Hosp_5	Stroke severity group_4. Moderate to severe
Hosp_6	Stroke severity group_5. Severe
Hosp_7	Stroke Type_I
Male	Stroke Type_PIH
Age	S2RankinBeforeStroke
80+	S2NihssArrival
Onset Time Known Type_BE	S2NihssArrivalLocQuestions
Onset Time Known Type_NK	S2NihssArrivalLocCommands
Onset Time Known Type_P	S2NihssArrivalBestGaze
# Comorbidities	S2NihssArrivalVisual
2+ comorbidotes	S2NihssArrivalFacialPalsy
Hypertension	S2NihssArrivalMotorArmLeft
Atrial Fib	S2NihssArrivalMotorArmRight
Diabetes	S2NihssArrivalMotorLegLeft
TIA	S2NihssArrivalMotorLegRight
Co-mordity	S2NihssArrivalLimbAtaxia
Antiplatelet_0	S2NihssArrivalSensory
Antiplatelet_1	S2NihssArrivalBestLanguage
Antiplatelet_NK	S2NihssArrivalDysarthria
Anticoag before stroke_0	S2NihssArrivalExtinctionInattention

There are additional SSNAP items which we would request for the proposed study including (but not limited to):

- Has it been decided in the first 72 hours that the patient is for palliative care?
- What was the initial brain imaging modality?
- Assessment of ischaemic penumbra by perfusion imaging
- Did the patient have any complications from the thrombolysis? (With further detailed fields)
- What was the patient's NIHSS score at 24 hours after thrombolysis / intra-arterial intervention?
- Has the patient had a TIA within the last month?
- What was the patient's Barthel score before the stroke?

SECTION 2: DETAILED QUALITATIVE PROTOCOL V1.0
26 SEPTEMBER 2019

This protocol has regard for the HRA guidance.

FULL/LONG TITLE OF THE STUDY

Use of simulation and machine learning to identify key levers for maximising the disability benefit of intravenous thrombolysis in acute stroke pathways (SAMueL)

SHORT STUDY TITLE / ACRONYM

SAMueL

PROTOCOL VERSION NUMBER AND DATE

Version number 1.0, 26th September 2019

RESEARCH REFERENCE NUMBERS

IRAS Number:	**260127**
SPONSORS Number:	1819/34
FUNDERS Number:	17/99/89

SIGNATURE PAGE

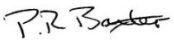
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:



Date:
26/09/2019

Name (please print): Ms Pam Baxter

Position: Senior Research Governance Officer

Chief Investigator:

Date:
26/09/2019

Signature:

Name: (please print): Ken Stein

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1. STUDY ORGANISATION

1.1 STUDY CONTACTS

Chief Investigator	*Professor Ken Stein* Institute for Health Research University of Exeter College of Medicine and Health

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Qualitative research lead	*Dr Julia Frost* Institute for Health Research University of Exeter College of Medicine and Health St Luke's Campus, Exeter EX1 2LU Phone: 01392 722970 Email: j.frost@exeter.ac.uk
Sponsor	University of Exeter Sponsor Representative *Ms Pam Baxter* Senior Research Governance Officer Research Ethics and Governance Office University of Exeter, Lafrowda House St Germans Road, Exeter EX4 6LT Phone: 01392 72 3588 Email: p.r.baxter2@exeter.ac.uk
Funder contact	Mr Nick Eaton Monitoring Programme Manager National Institute for Health Research Evaluation, Trials and Studies Co-ordinating Centre (NETSCC) University of Southampton Alpha House, Enterprise Road

	Southampton SO16 7NS Phone: 02380595593 Email: nick.eaton@nihr.ac.uk
Key Protocol Contributors	*Dr Kristin Liabo* Institute for Health Research University of Exeter College of Medicine and Health St Luke's Campus, Exeter EX1 2LU Phone: 01392 722895 Email: k.liabo@exeter.ac.uk *Dr Julia Frost* Institute for Health Research University of Exeter College of Medicine and Health St Luke's Campus, Exeter EX1 2LU Phone: 01392 722970 Email: j.frost@exeter.ac.uk *Dr Mike Allen* Institute for Health Research University of Exeter College of Medicine and Health St Luke's Campus, Exeter EX1 2LU Phone: 01392 726080 Email: m.allen@exeter.ac.uk
Committees	**Study Steering Group:** Ken Stein, Mike Allen, Julia Frost and Kristin Liabo (contact details as above); Sponsor Representative, or their deputy. *Professor Richard Everson* Computer Science University of Exeter College of Engineering, Mathematics and Physical Sciences

	Phone**:** 01392 724065 Email: R.M.Everson@exeter.ac.uk *Mr Leon Farmer* - Patient representative *Professor Martin James* Consultant Stroke Physician Royal Devon & Exeter Hospital NHS Foundation Trust/University of Exeter Medical School Exeter EX2 5DW Phone: 01392 406070 *Ms Penny Thompson* - Carer representative *Dr Zhivko Zhelev* Institute for Health Research University of Exeter College of Medicine and Health St Luke's Campus, Exeter EX1 2LU Phone: 01392 726093 Email: z.zhelev@exeter.ac.uk **External Advisory Group:** *Dr Thomas Monks* University of Southampton Health Sciences University Road Southampton SO17 1BJ thomas.monks@soton.ac.uk Professor Anthony Rudd Consultant Stroke Physician

	Guy's and St Thomas' NHS Foundation Trust Phone: 020 7188 2515 (Secretary Sandra Gray) Email: anthony.rudd@kcl.ac.uk Professor Gary Ford Oxford Academic Health Science Network Magdalen Centre 1 Robert Robinson Avenue Oxford OX4 4GA gary.ford@ouh.nhs.uk **Patient and Carer Involvement group:** Leon Farmer and Penny Thompson (contact details via Clinician contact as provided above) Other members will be invited closer to the time of the first involvement group meeting.

1.2 STUDY SUMMARY

Full study Title	Use of simulation and machine learning to identify key levers for maximising the disability benefit of intravenous thrombolysis in acute stroke pathways (SAMueL)
Short title	Machine learning to maximising benefit of thrombolysis in acute stroke (SAMueL)
Study Design	Computer modelling of audit data, qualitative interviews
Study Participants	Anonymised SSNAP data from stroke patients. This data will only be available to Mike Allen under a formal data sharing agreement with HQIP, and will not be shared with other research team members

	(quantitative component) Physicians involved in stroke care – participation in interviews and focus groups (qualitative component)
Planned Size of Sample (if applicable)	The quantitative research will use anonymised data from ~225,000 patient records (SSNAP dataset) In the qualitative research we will interview 30-40 physicians involved in NHS Trust stroke care, and potentially use summaries of anonymous notes that will be obtained via a workshop with 30 current patient and physician stakeholders, identified during the course of this research and contingent on the preliminary findings. .
Follow up duration (if applicable)	N/A
Planned Study Period	October 2019 – January 2021
Research Question/Aim(s)	This study has two components. The quantitative part is a modelling study which will use anonymised data from the SSNAP database to: 1) Create a generic stroke thrombolysis pathway simulation model that could be readily applied to any NHS Hospital Trust 2) Extend the analysis to include factors other than door-to-needle times, with special focus on differences in clinical decision making as analysed and modelled with machine learning techniques Qualitative methods will be used to: 1) Explore current attitudes and rationale for the use of thrombolysis for ischaemic stroke, in order to establish reasons for the variance in the use and speed of thrombolysis. 2) Elicit physician perspectives on simulation and machine learning feedback, to understand how our results are best presented in a way that is useful and likely to have an impact on their practice. 3) Identify potential routes for the implementation of machine learning feedback, to inform and improve future stroke management. 4) Explore and anticipate possible unintended consequences of stroke pathway changes.

1.3 FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health Research Health Services and Delivery Research (HS&DR) programme	**£329,261.20**

1.4 ROLES AND RESPONSIBLITIS

1.4.1 Role of study sponsor and funder

The University of Exeter is the sponsor of this study. As employees at the University of Exeter the named researchers on this study are contractually bound to adhere to the University's ethical policies and governance structures.

Role of Sponsor

The study sponsor will ensure that the research team has access to resources and support to deliver the research as proposed and that responsibilities for management, monitoring and reporting of the research are in place prior to the study commencing. The sponsor will ensure that there is agreement on recording, reporting and reviewing significant developments as the research proceeds and approve any modifications to design, obtaining requisite regulatory authority.

The sponsor will assume responsibility for operating the management and monitoring systems of the research.

Prior to the study commencing the sponsor will be satisfied that:

- The research will respect the dignity, rights, safety and well-being of participants and the relationship with healthcare professionals.
- Where appropriate the research has been reviewed and approved by an NHS Research Ethics Committee and/or the Health Research Authority Approval Programme.
- The Chief Investigator, and other key researchers have the requisite expertise and have access needed to conduct the research successfully.
- The arrangements and resources proposed for the research will allow the collection of high quality, accurate data and the systems and resources will allow appropriate data analysis and data protection.

- Organisations and individuals involved in the research agree the division of responsibilities between them.
- Arrangements are in place for the sponsor and other stakeholder organisations to be alerted to significant developments during the study, whether in relation to the safety of individuals or scientific direction.
- There are arrangements for the conclusion of the study including appropriate plans for the dissemination of findings.

The sponsor plays no role in the design of this study, and will have no role in data analysis or interpretation, or writing up of findings of the study.

The full work will be submitted to the funder (NIHR) for publication in Health Services and Delivery Research (ISSN: 2050-4537). For any other publications we will alert NIHR prior to publication (after acceptance of publication).

Role of the Funder

The research funder has the responsibility to ensure that there is a proper use of the funds they control. The study is funded by the NIHR HS&DR stream. The Funder has reviewed the programme/study plan of the research and established that the research is worthwhile, of high scientific quality and represents good value for money. The research funder has assessed the experience and expertise of the Chief Investigator, other key researchers on the programme and has deemed that there is appropriate infrastructure for the research to be carried out.

The funding review process provided feedback on the design of the programme/study plan. The funder plays no further role in the design of this individual study and will have no role in data analysis or interpretation, or writing up of findings of the study. The funder will be sent all outputs prior to dissemination, but has no role in the decision to submit for publication.

1.4.2 Roles and responsibilities of study management committees/groups & individuals

- Study Steering Group

Members: Chief investigator, all co-applicants, two patient and carer collaborators, Sponsor representative or their deputy.

Frequency: Three-monthly meetings, with intermittent ad-hoc meetings if necessary and deemed so by study progress and activities.

Aim: To ensure study progress in regards to the three main parts of the study (simulation, machine learning, and qualitative research).

- External Advisory Group

Members: Chief investigator, four research/ clinical experts' external to the study

Frequency: Three meetings over two years

Aim: To provide researchers with advice on how to address any problems or challenges that might emerge throughout the lifetime of the study, and to advice on the implications of the research findings for dissemination and impact work.

- Patient & Carer Involvement Group

Members: People who have experienced a stroke and people caring for someone after a stroke

Frequency: Four meetings over two years

Aim: This group will work with the researchers on the visual displays from the modelling research. They will also help analyse the findings from the simulation and be part of the discussion on how the decision-making tool might take patients' views on risk/benefit into account. This group inform the planning of the stakeholder event at the end of the study. Two members of this group will also sit on the Study Steering Group.

1.4.3 Protocol contributors

Senior researchers on this study, Kristin Liabo and Julia Frost, have provided qualitative expertise to the design of the protocol, which was based on the funding application and the project plan; which received contributions and reviews from the whole study team, led by Mike Allen.

Mike Allen also reviewed and provided comment on this protocol, and contributed the main documents on which the study is based.

Professor Ken Stein as Chief Investigator leads the study and has reviewed and approved this qualitative protocol.

1.5 KEY WORDS

Stroke, thrombolytic therapy, modelling research, machine learning, qualitative research, implementation science

1.6 TIMELINE OF ACTIVITIES

Timeline	Simulation and machine learning research	Qualitative research	Patient and public involvement (PPI)	Stakeholder event and disseminatio n	Timeline
Feb 2019	Data preparation	Ethics application			Feb 2019

Timeline	Simulation and machine learning research	Qualitative research	Patient and public involvement (PPI)	Stakeholder event and disseminatio n	Timeline
Mar 2019	s and refine regional model. Application for access to SSNAP data.	and development of study materials	Invitations to PPI group (2-3 patients, 2 –3 carers)		Mar 2019
April 2019					April 2019
May 2019			Training		May 2019
Jun 2019					Jun 2019
Jul 2019	First visuals ready for PPI meeting		Meeting about visualisation of base models		Jul 2019
Aug 2019					Aug 2019
Sept 2019	Access national data	Seek HRA/ REC Approval			Sept 2019
Oct 2019	Data preparation	Pilot interviews (n=3) + interview (n=4) with consultants in the SW region Focus groups (N=1, 2 or 3) about base model visuals			Oct 2019
Nov 2019	Modelling research				Nov 2019

Timeline	Simulation and machine learning research	Qualitative research	Patient and public involvement (PPI)	Stakeholder event and dissemination	Timeline
Dec 2019		Individual interviews nation-wide about the modelling research	Catch up meeting		Dec 2019
Jan 2020					Jan 2020
Feb 2020					Feb 2020
Mar 2020					Mar 2020
Apr 2020	Analysis and start preparation for final report				Apr 2020
May 2020		Contingent on previous work, focus groups 4-5 with physicians nation-wide about base model visuals			May 2020
Jun 2020		Individual interviews nation-wide about the modelling research	Meeting about research findings		Jun 2020
Jul 2020					Jul 2020
Aug 2020		Data analysis and writing up	Meeting to plan input at stakeholder workshop	Invitations to stakeholder workshop	Aug 2020
Sep 2020					Sep 2020
Oct 2020	Draft journal articles		Meeting to discuss further		Oct 2020

Timeline	Simulation and machine learning research	Qualitative research	Patient and public involvement (PPI)	Stakeholder event and disseminatio n	Timeline
			dissemination		
Nov 2020				Stakeholder workshop	Nov 2020
Dec 2020	Dissemination: conferences, NHS newsletters, meetings, academic journal articles, creative and social media outlets.				Dec 2020
Jan 2021					Jan 2021

2. STUDY PROTOCOL

Use of simulation and machine learning to identify key levers for maximising the disability benefit of intravenous thrombolysis in acute stroke pathways

2.1 BACKGROUND

Our aim is to use computer-based technologies to understand how we can improve thrombolysis use and speed. We want to develop this analysis so that it can be run as part of the routine quarterly national stroke audit, thereby further assisting stroke physicians in their decision-making. Qualitative research will be undertaken to maximise the acceptance and influence of these techniques.

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 disability-adjusted life years in the UK over the last 25 years.[3] Currently the only licensed drug treatment for acute stroke is thrombolysis with Alteplase, the benefit of which is critically time-dependent[4] with little or no benefit after 4.5 hours from stroke onset. Over the fifteen years since European licencing, the population benefit from thrombolysis has been limited by slow uptake of the treatment, and in-hospital delays to the administration of thrombolysis.[5-7]

In England, Wales and Northern Ireland the national stroke audit 'SSNAP' (see Section 2.2) records that 11.2% of acute stroke patients receive thrombolysis, but use in individual acutely admitting stroke centres varies from 0 to 24.5%.[2] The lowest 10% of acutely admitting stroke teams administer thrombolysis to fewer than 5.9% of patients, whereas the top 10% administer thrombolysis to more than 16.7%. Time from arrival to thrombolysis ('door-to-needle') also varies significantly. The fastest 10% of hospitals have door-to-needle times of 40 minutes or less, whereas the slowest 10% have door-to-needle times of 85 minutes or more.[2] There is therefore considerable variation between hospitals in the use, and speed, of thrombolysis for acute stroke patients, and the overall use of thrombolysis and the high inter-hospital variation has not changed in the last four years.

There have been many studies of factors that influence the uptake of thrombolysis.[8-13] Eissa et al. divided barriers into pre-admission and post-admission phases.[8] Pre-admission barriers included poor patient response (not recognising symptoms of a stroke and not calling for help soon enough) and paramedic related barriers (such as adding delays in getting the patient to an appropriate hospital in the fastest possible time). Hospital-based barriers include organisational problems (delay in recognising the type of stroke the patient is presenting with, delays in pathway, poor infrastructure) and physician uncertainty or lack of experience leading to low use of thrombolysis. There has been significant discussion on how services may best be organised to optimise the effectiveness of thrombolysis.[14] This is to limit the variability of thrombolytic practises.

Analysis of patient pathway data coupled with computer simulation has previously allowed investigation and improvement of thrombolysis use in individual hospitals - increasing both the number of patients treated and reducing door-to-needle times.[15 16] These models have usually focused solely on the speed of the acute stroke pathway from arrival at hospital to treatment with thrombolysis.[16] Interest in the use of simulation for improving the performance of the acute stroke pathway has reached an interest such that a common framework has been proposed[17]; one which pays attention to the implications of any service re-configurations.

Pathway modelling based on simulating process steps allows for good simulation of the speed of the stroke pathway, but cannot easily model differences in clinical decision making. We will test whether a model can dissect out the variation in thrombolysis rate that is dependent upon differences in patient populations (e.g. age or stroke severity) in different hospitals, and from the differences that are dependent on the culture of decision making at different hospitals (e.g. more cautious vs more aggressive clinical decision making). A variety of machine learning techniques now exist[18], which are able to make good predictions on pre-existing multidimensional data over a binary or categorical outcome variable (such as whether a patient receives thrombolysis or not). These have the potential to add modelling of clinical decision making to a model of the acute stroke pathway, with the aim of predicting what decision (to thrombolyse or not) would be made for the same patient in different hospitals. Models may also be trained on a reference standard set of hospitals (regarded as centres of clinical excellence) and use of thrombolysis for any patient predicted using that ‘benchmark clinical decision making model’.

Machine learning has three key advantages for our approach: 1) it may use a variety of techniques (ranging from more traditional statistical regression models through to state-of-the-art Deep Learning Neural Networks) which may be combined into one outcome using a technique known as ‘ensemble learning’, 2) Machine Learning is highly scalable, with a framework developed for dealing with very large numbers of patients each of which might have very many ‘features’ recorded. Models may, for example, in time be scaled to also make use of any imaging data available, 3) Machine Learning models may continually learn from new data without having to re-fit all previous and recent data together.

In this study, physicians will be integral to helping us to understand how the research findings can best be used to inform practice. In a qualitative component to the research we will interview 30-40 physicians and run three focus groups with 5-8 physicians. In these individual and group interviews we will ask about physicians’ decision-making in regards to thrombolysis, what implications they see from changing the patient pathway and about the usefulness of machine learning to assist decision-making.

2.2 RATIONALE

As detailed above there is considerable and persistent variation in the use and speed of thrombolysis, a time-critical treatment for stroke, which limits benefit to individuals and the population from this cost-effective treatment. We will work with the Sentinel Stroke National

Audit Programme (SSNAP) as key partners to model their existing data and enhance their audit processes, by combining their existing audit methodology with pathways and machine learning. Advances in national audit data collection, and advances in scalable computational methods for pathway simulation and machine learning make this a timely project to introduce these advanced analytical tools into SSNAP's quarterly national stroke audit reports. We further need to advance our understanding on how to use models and visual aids from this work with physicians, to enable utilisation of the research in practice.

The research therefore consists of three key components, all relating to the use of thrombolysis in the acute stroke pathway:

1) Stroke pathway simulation.
2) Patient level machine learning model on decision whether to administer thrombolysis (when there is time to administer thrombolysis).
3) Qualitative research with an implementation focus, exploring how physicians perceive the risks and benefits of using machine learning during audit to improve thrombolysis use for ischaemic stroke.

2.3 RESEARCH AIMS AND OBJECTIVES

2.3.1 Simulation and machine learning

For the simulation and machine learning part of the study our aim is to extend previous work on stroke thrombolysis pathway simulation in three significant ways:

1) To create a generic stroke thrombolysis pathway simulation model that could be readily applied to any NHS Trust hospital.
2) To extend the analysis to include factors other than door-to-needle times, with special focus on differences in clinical decision making as analysed and modelled with machine learning techniques
3) To use a modelling framework that is open source and fast enough to run routine analysis on all UK hospitals. We will also structure the model to make it suitable for extension to include mechanical thrombectomy, an emerging treatment for the most severe form of ischaemic stroke.

The combined simulation and machine learning would then be used in the quarterly national stroke audit, estimating the potential use of thrombolysis and the associated clinical benefit, by improving pathway speeds and processes, and by applying clinical decision making similar to the benchmark centres of clinical excellence. The purpose is to improve rates and speed of thrombolysis, by improving audit methodology. By applying machine learning model in an audit setting, though valuable alone, may also potentially lead to 'expert' advisory systems that may support clinical decision making (especially by less experienced clinicians).

2.3.2 Qualitative research

A critical question of applying this type of advanced computational techniques is 'will the feedback change clinical practice for the better?' Qualitative research will be conducted with an overall objective to determine physician perspectives and concerns towards the use of simulation and machine learning. The qualitative interviews will review and explore the conduct of clinical practice in stroke thrombolysis. This will also help highlight what factors are important in communicating the model results. Qualitative methods will be used to:

1) Explore current understanding and rationale for the use of thrombolysis for ischaemic stroke, in order to establish reasons for the variance in the use and speed of thrombolysis.
2) Elicit physician perspectives on simulation and machine learning feedback, to understand how our results are best presented in a way that is useful and likely to have an impact on their practice.
3) Identify potential routes for the implementation of machine learning feedback, to inform and improve future stroke management.
4) Explore and anticipate possible unintended consequences of stroke pathway changes. The simulations can lead to pathway changes if we identify one or two key areas that any one hospital needs to focus on, in order to optimise their thrombolysis use.

2.3.3 Research outputs

We have four production aims:

1) To produce computer code that will be routinely used by the national stroke audit SSNAP as part of their quarterly outputs to participating hospitals and commissioning groups, and in national reports. The code will have a structure for potential future extension to mechanical thrombectomy (an emerging alternative to thrombolysis for the most severe ischaemic strokes).
2) To publish the code in a public Open Source code repository (e.g. GitHub or GitLab)
3) To write articles (in addition to the NIHR monograph) on:
    - Application of machine learning to audit of thrombolysis use (technical machine learning publication)
    - Application of combined simulation and machine learning to stroke thrombolysis audit (suitable for general/clinical readership)
    - Physicians' attitudes to use of computer simulation and machine learning in national audits, and physicians' views on thrombolysis use, which are currently unexplored (suitable for general/clinical/managerial readership)
4) Presentation of above themes at the UK stroke forum and an international stroke conference

In addition we will respond to dissemination ideas created at the stakeholder workshop, and use social media and professional's newsletters (i.e. through medical insurers) to cascade information about the above outputs and the study findings.

2.4 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

The research consists of four key components, all relating to the use of thrombolysis in stroke patients:

1) Stroke pathway simulation using regional (first) and national (second) data provided by our partners, the Sentinel Stroke National Audit Programme (SSNAP).
2) Patient level machine learning model on decision whether and when to administer thrombolysis, using national data from SSNAP.
3) Qualitative interviews with physicians, individually and in groups, about how they perceive the risks and benefits of thrombolysis, and of using machine learning during audit to optimise thrombolysis use for ischaemic stroke.
4) Facilitated discussions between stakeholders, identified during the course of the research, on the preliminary findings from the study at a workshop.

2.4.1 Data collection

a) Quantitative research

The stroke pathway simulation and machine learning will use data from SSNAP. SSNAP is the prospective national stroke audit of in-patient stroke care in England, Wales and Northern Ireland, funded by the Healthcare Quality Improvement Partnership (HQIP) and hosted by the Royal College of Physicians of London and King's College London. SSNAP provides an opportunity to train models using data from all acute stroke hospitals in England, Wales and Northern Ireland, extracting learning at both the generic and local level, with the ability to feedback, through the established quarterly audit process, to all hospitals.

All qualitative work will be based on results generated using synthetic data. Synthetic data is data that is generated to look and behave like authentic patient-level data, but is not the result of obfuscation ('jittering') of authentic data (a synthetic data point is not the product of manipulation of an original authentic data point).

Synthetic data will be produced using one or more of the following methods:

- Parametric co-variance sampling model
- Variational AutoEncoders (VAEs)
- Generative Adversarial Networks (GANs)

Professor Anthony Rudd on our External Advisory Group and co-applicant and Study Steering Group member Martin James are both members of the SSNAP Intercollegiate Stroke Working Party.

b) Qualitative research

The qualitative research will collect data through individual and group interviews with physicians involved in stroke care. These will be conducted by an experienced qualitative researcher.[19]

First, individual (N=7) and group interviews (N=3) will be conducted locally in regional stroke centres (South West of England) in order to determine different clinician approaches and attitudes to the management of ischaemic stroke and thrombolysis practice.[20] These groups (N=5-8 per group) will enable us to identify and pilot a range of visual displays and other methods of feedback from both pathway modelling and machine learning for use in individual interviews. We anticipate that these will involve: 1) national anonymised data, 2) regional anonymised data and 3) individual anonymised case data (or patient-based 'vignettes'), to enable us to elicit perspectives and views about how best to present the feedback derived from machine learning.

Second, individual and group interviews will be undertaken nation-wide with 20-30 physicians, both career and training grades. Whether we conduct individual or group interviews, or both in a site will be informed by the preferences of staff who agree to take part in the study.

The individual and group interviews will follow the same format. A topic guide will be used in a two-part interview lasting approximately 60 minutes. The first half of the interview will ascertain which factors inform and influence clinical decision-making and beliefs about the appropriate use of thrombolysis, or not. This is to capture the context in which decisions are made. This is also to understand better what data needs to be captured by SSNAP in the future, so that we can know better what decisions to base modelling and machine learning on.

We will start by asking questions about the treatment decision-making in a small number of made-up vignettes, based on anonymous data from the SSNAP database. The questions will then focus on the physician's or clinical team's decision-making in regards to thrombolysis, and whether SSNAP captures the most important data from this. We will not be asking for personal information about individual patient cases. The purpose is first and foremost to understand what kind of data needs to be captured for SSNAP, and we believe this is possible without in-depth knowledge of real cases. The vignettes will be a starting point for exploring attitudes, experiences and concerns of physicians.

This part of the interview will also explore views on what unintended consequences may come about from changing the acute stroke pathway, and how such adverse effects might be detected and mitigated.

In the second part of the interview we will introduce the data displays developed from the regional focus groups, and ask which forms of data visualisation can best inform clinical practice.

All interviews will be audio recorded, transcribed verbatim and anonymised. Only professional transcribers will be used and they will be asked to sign a confidentiality or Non-Disclosure Agreement before commencing any work. The interviews will not contain any identifiable data.

A workshop will be conducted three months prior to the study's end, and up to 30 stakeholders will be invited to participate, which will include the patient and carer members of the study advisory groups, health professionals (physicians and members of the wider stroke

team) and NHS managers. The workshop will follow a structured format where participants engage in focused discussions, which will be guided by presentations of preliminary research findings from the qualitative and quantitative research teams and SSNAP, and the views of involved patients and carers who have worked with the researchers on the study as partners in the research. We will present early findings from the various aspects of the research, including both the simulation and machine learning, and the focus groups and interviews.

Members of our patient and carer involvement group will also inform workshop participants about their contribution to the overall research project. Contingent on the nature of preliminary findings, and to identify any group consensus perspectives, activities will initially be in separate groups of professionals, patients, and others, followed by mixed groups of people from different backgrounds.

This process and the multiple perspectives will be recorded in several ways, 1) by note-takers within sessions, 2) the researchers' participant observation notes made immediately after the stakeholder workshop and 3) participants' flipchart notes and summaries made during all sessions.

2.4.2 Data analysis

The quantitative data analysis will be exploratory and this protocol therefore outlines starting points for the analysis rather than detailed description of every step. Because of the sequential steps of simulation modelling and machine learning the quantitative analysis might change due to intermediate findings.

A: Pathway simulation model analysis

The pathway simulation model is coded in Python/NumPy and is based on sampling from distributions based on real-world data. Patients pass from one process stage to the next (stroke onset, arrival at hospital, CT scan, decision to administer thrombolysis, administer thrombolysis). The time spent in each stage is based on sampling from distributions derived from SSNAP data.

For a patient to receive thrombolysis in the pathway model they must meet the following criteria: 1) stroke onset time known, 2) arrival at hospital within 4 hours of stroke onset, 3) have an ischaemic stroke and be judged to be eligible for thrombolysis, and 4) be within the licenced thrombolysis time window (4.5 hours and 3 hours onset-to-treatment time for patients aged under and over 80 respectively), when summing the process step times in the model. If a patient receives thrombolysis in the model then the probability of an additional good outcome (modified Rankin Scale [mRS] 0-1, no significant disability and able to carry out all usual activities) due to use of thrombolysis is calculated from the onset-to-treatment time and is based on the meta-analysis by Emberson *et al.*[4]

If the pathway model is run without the machine learning thrombolysis component (see next section), the likelihood of being given thrombolysis if scanned within 30 minutes is taken either from the hospital's own anonymous data on the proportion of patients who have time to

receive thrombolysis (30 minutes licence window remaining after scan) and are given thrombolysis, or by using a published reference proportion (e.g. in the IST-3 trial 50% of stroke patients, if scanned with time left to treat, went on to receive thrombolysis).[21]

Model outputs: The primary outputs of the model are 1) an estimate of the proportion of patients receiving thrombolysis, and 2) expected clinical benefit achieved through use of thrombolysis (additional disability-free patients).[22] Specifically what the model predicts is how changes in the process or decision-making will effect thrombolysis use and benefit.

Model Validation: In order to validate the model, 3 years data (~225,000 patient records) will be split into two sets: Model parameters will be set using 75% of the data, and accuracy of the model compared with 25% test data not used for model training.

Scenario analysis: The model will be run for each hospital with key changes in the pathway, e.g. using upper quartile SSNAP data for determining stroke onset time, arrival-to-scan time, scan-to-treatment time, and the proportion of patients (with time left to treat) with decision to thrombolyse.

B: Clinical decision model analysis (machine learning)

The clinical decision model aims to replicate the decision whether to give thrombolysis for any given patient at any given hospital. If patient characteristics are kept unchanged, but the admission hospital is changed, the model should predict different expected decisions for the same patients in different hospitals. Differences in decisions between hospitals may be compared by passing the same randomly selected sample of patients to all hospitals (as differences between observed thrombolysis utilisation between different hospitals may be complicated by differences in patient characteristics between different hospitals).

The model may be trained using different benchmarks. For example the model may be trained using a subset of hospitals recognised for their clinical excellence in acute stroke care (optimal thrombolysis). Possible subsets include hospitals in London which were found, as a group, to have improved outcomes following stroke care reorganisation/centralisation[23], or subgroups identified within the national audit with other organisational characteristics of excellence (for example, high rates of direct admission to an acute stroke unit, high rates of early dysphagia screening).

This model is intended to make decisions based only on clinical presentation, assuming that there is sufficient time remaining in which to assess and give thrombolysis. Patients are included if they have been scanned with 30 minutes remaining in the licence window to give thrombolysis. The model is coded in Python using available SciKitLearn, Tensorflow, and PyTorch machine learning libraries.

The model predicts whether an individual patient should receive thrombolysis or not from a set of 50 parameters defining the patient's characteristics, clinical well-being, and hospital attended (see section on pilot work for a list of features used in the pilot work), that would all

be available to the stroke clinician at the time of their thrombolysis use decision-making. The models are supervised learning models based on a training set of data with known use of thrombolysis. The machine learning models to be used are:

- Random Forests
- Support Vector Machines (SVM): linear and rbf
- Neural network (including basic freed-forward neural networks, and more advanced PyTorch and/ or Tensoflow neural networks).
- Logistic regression
- K nearest neighbours
- Gaussian process models
- Novel decision-tree methods (based on application of current work ongoing at the University of Exeter).

In addition to single type machine learning models, ensemble models will be built. These take the output from multiple different machine learning models and have been shown to be able to produce better accuracy than any single method alone(18).

Model outputs: The model outputs for each patient record entered whether thrombolysis would be given (along with a measure of probability of the decision).

Model Validation: In order to optimise and validate the model, 3 years data (~225,000 patient records) will be split into three sets (randomly selected from stratified data to ensure all sets have similar over thrombolysis use). 75% of the data will be used for model development, and 25% of the data will be held back for model testing and validating.

Model scenarios: The aim of model scenarios is to ask ‘what if?’ questions of the model, to test the expected effect of hypothetical changes to the system.

A reference set of anonymised patient data from SSNAP may be passed to each of the models that are trained on decisions made for patients from a single hospital, and thrombolysis use can be predicted for each hospital on this common reference set of patients. This will help identify hospitals that appear to have unusual thrombolysis use decisions (either significantly higher or lower than average, or significantly different to a benchmark group) independent of differences in patient populations attending each unit.

Where clinical decision making appears to significantly differ from benchmark hospitals, a cohort of patients from a single hospital (non-elite) may be passed to a model trained on patients from a benchmark set of hospitals (recognised by their clinical excellence, based on SSNAP grading of acute care). That way, the use of thrombolysis within the non-elite centre (the recorded thrombolysis use) can be compared with the potential decision-making as would have happened for that patient if they attended an elite centre (modelled thrombolysis use). To aid audit, a small group of cases (of anonymous patients) will be identified for each hospital where modelled (based on the model trained using the benchmark set of hospitals) and actual thrombolysis use differ.

Our pilot studies give a strong indication of the robustness of the machine learning methods. Nevertheless if these initial results are not borne out over particular time epochs or at particular hospitals we will investigate the reasons, for example, if there is a difference in practice between pilot hospitals. This will give insight into the practice of the stroke treatment pathway and we will construct alternative models to model these data.

As an example, if accuracy is lower than anticipated, the results of individual machine learning models may be compared. If models differ from each other the most likely issue is that the models are each too weak, in a random fashion, to attain high accuracy. In this case increasing the number of models used, and combining results (an 'ensemble of weak learners') offers a popular approach to improving accuracy. If accuracy is low but different models agree on the decision then this points to a systematic difference between model and data (for example one clinician in any one centre always making a different type of decision than other clinicians in that centre), and further investigation should focus on what additional data should be collected to improve accuracy (e.g. collecting data at clinician level in this hypothetical example).

The machine learning model may be used independently, but may also be combined with the pathway simulation mode. The combined model allows for investigation of the potential benefits of improving pathway processes and applying clinical decision making aligned with centres of clinical expertise. The combination may therefore provide a useful and realistic target use of thrombolysis given a hospitals own patient group characteristics.

C: Qualitative data analysis

The anonymised data from interviews and the notes from the stakeholder workshop will be held on a password protected folder on the secure University of Exeter server. The data analysis will be managed in NVivo 11.

A thematic analysis of interviews and the stakeholder workshop notes will be conducted.[24] The analysis will be iterative, moving between data collection and analysis to test emerging theories. This work will build upon previous research findings on the use of thrombolysis[12], and will focus on the implementation of feedback from machine learning to optimise thrombolysis decision-making for ischaemic stroke management. We anticipate that this might involve the identification of examples of best practice that could inform the development of a future intervention to support quality improvement activities all along the pathway.[25] Another possible output could be the development of a typology concerning the type of visualisation that might work best in a given scenario, e.g. whether they are organisational, clinician or patient factors.

Our analysis will be sensitive to whether clinicians raise concerns about any changes to the acute stroke pathway or decision-making, following use of the models from our quantitative work. We will produce a summary from the interviews with physicians about potential unintended consequences from changing the acute stroke pathway, and how such adverse

effects might be detected and mitigated. These points will then inform a Failure Mode Effects Analysis (FMEA) as used in engineering when trying to anticipate what may go wrong with a product.

Thematic analysis of the workshop data will augment and triangulate preliminary findings from the interviews, to inform the development of an intervention to support quality improvement in thrombolysis practice. Previous experience with this method suggests that it will contribute concerns and issues and offer additional interpretations and suggestions for implementation.[26] [27]

2.5 STUDY SETTING

The computer modelling will use data from all English and Welsh units registered as acutely admitting stroke units in SSNAP but the modellers will not visit these sites.

Qualitative interviews will be held with physicians from acute stroke units and emergency departments in England and Wales. It is important to the research that interviews are held with a wide range of physicians and that this range reflects the variety of thrombolysis use across hospitals, who administer the treatment, average door to needle time, and whether it is a specialist stroke unit or not. Individual and group interviews will be held at the place of work of the participating physicians. We expect the interviews to last approximately one hour.

The stakeholder workshop will be held at a suitable venue, this might be at a conference facility near a hospital site or at the university, or it might be hired from a commercial vendor. The venue will be selected on the basis of its accessibility to participating stakeholders.

2.6 SAMPLE AND RECRUITMENT

For the modelling work all patient data will be from a single source: Since inception in 2013, SSNAP now has over 300,000 case records from 127 acutely admitting hospitals. SSNAP has near-complete coverage of all acute stroke admissions in the UK (outside Scotland). All hospitals admitting acute stroke participate in the audit, apart from Leeds, and year-on-year comparison with Hospital Episode Statistics confirms estimated case ascertainment of 95% of coded cases of acute stroke. We will access data through a single source managed by HQIP. This anonymised data will be handled in accordance with GDPR and DPA 2018 policies.

For the qualitative work we will recruit physicians through existing networks and study collaborators, and via the NIHR Clinical Research Network's Stroke Network. Invitees to the stakeholder workshop will be physicians involved in stroke care and NHS managers from participating hospital NHS Trusts, and the patients and carers involved in the study in an advisory capacity.

2.6.1 Eligibility Criteria

In the modelling work the researchers will work with a criterion called 'eligible for thrombolysis'. This is the proportion of ischaemic stroke patients (arriving within 4 hours of known stroke onset, and scanned within 4 hours of arrival) who are considered clinically

eligible for thrombolysis. This figure is obtained by examining the proportion of ischaemic stroke patients who are scanned with at least 30 minutes left to thrombolyse who are given thrombolysis.

Physician's eligible to be interviewed individually or taking part in focus groups will have to be employed as at an NHS hospital and be involved in delivering stroke treatment at the time of the interview.

2.6.2 Sampling

The quantitative modelling will use 3 years data (~225,000 patient records) from SSNAP.

Publicly SSNAP ratings will be used to sample physicians for the qualitative interviews. Using these ratings, researchers will group hospitals based on their rates of thrombolysis, average scan time and quality scores, ordering them into three groups and randomly select sites within each group. The qualitative researchers will further use maximise variance sampling to ensure inclusion of a range of relevant models of delivery and physician experiences within these ranges.

The sampling frame below shows the key characteristics of physicians interviewed in individual and focus group interviews. These are not mutually exclusive and will overlap within individuals and teams that we interview. Our main sampling characteristic is use of thrombolysis. Through the study recruitment form we will also sample across the other characteristics listed below.

Model of delivery	Thrombolysis use top 20% of SSNAP audit N=10	Thrombolysis use bottom 20% of SSNAP audit N=10	Other cases of interest as identified through individual interviews. N=10	
Physician specialism	Stroke	Emergency or acute care	Geriatric medicine	Neurology
Physician grade	Consultant	Staff doctor	Specialty trainee	Other
Door to needle time (average minutes for place of work)	40 minutes or less	41-84 minutes	85 minutes or more	

Mid-way through data collection we will do an interim analysis of individual interviews to establish whether we are fulfilling the sampling frame, and whether the sampling frame is fit for purpose. If necessary, the sampling frame will be adjusted to change or add to the characteristics, or shift the numbers needed per characteristic.

Size of sample

The quantitative modelling will use 3 years of data (~225,000 patient records) from SSNAP. This number is chosen to optimise the computer modelling work and base it on comprehensive national data.

The qualitative researchers will conduct interviews with 30-40 physicians, both career and training grades. Focus group size will depend on the team involved and how many physicians can spare time to the study. The stakeholder workshop will be for approximately 30 people. These numbers are chosen to enable meaningful in-depth data collection which will result in a manageable dataset appropriate to the size and resourcing of this study.

Sample identification and recruitment

All data for the quantitative research comes from SSNAP and is collected as part of routine care. We will access data through a single source managed by HQIP. SSNAP data access was granted by HQIP on August 14th 2019.

Physicians identified as eligible for the qualitative interviews through portfolio adoption by the Clinical Research Network will be contacted by research nurses from their local NIHR CRN Stroke Network, and not by the qualitative researchers. Publically available SSNAP data (https://www.strokeaudit.org/results) will enable us to identify the extent of thrombolysis use across hospitals, and therefore identify sites of particular interest to the qualitative arm of our study (centres with high or low use of thrombolysis).

The contact letter or email to eligible physicians will include a study recruitment form (consent to be contacted). On receipt of this information the qualitative researchers will consult the sampling frame and contact eligible physicians to be interviewed.

Recruitment to the pilot interviews will be through personal contacts who have agreed access in principle. We will approach teams of registrars and aim for interviews to coincide with their team meetings. The first group will be with co-investigator Professor Martin James' team at the Royal Devon and Exeter Hospital, at a time when the registrars meet regularly. We will pilot the group interview schedule with this team. We will then recruit stroke registrars to group interviews at Plymouth's Derriford Hospital and Torbay Hospital.

Invitations to the stakeholder workshop will be extended to physicians who have been interviewed for the study or expressed an interest in the study, people in managerial positions in services providing the stroke pathway, and members of our patient and carer advisory group. The purpose of the stakeholder workshop is to maximise the range of feedback and capturing of differing perspectives.

2.6.3 Consent

When someone expresses an interest in being interviewed for the study (they complete and sign a study form if they chose to provide consent to be contacted), they will receive further written information about the research, the format of the interview and what it entails (Appendix 1a-c). A time will be agreed for the potential participant to speak to the researcher on the phone about the information they have received, to give them a chance to ask questions. At this point it will be agreed with the potential participant, whether the participant will be interviewed individually or in a group (their team). After the potential interviewee has had a chance to ask questions about the study, they will be asked if they would be willing to be interviewed and an interview date and time will be agreed. On the day of the interview the potential participant will be asked if they have any questions before being asked to fill in and sign the written consent form (Appendix 1d). The interview will not commence before written consent has been obtained.

The consent procedure will emphasize people's rights to withdraw from the study at any time.

The consent procedure will further outline people's ability to withdraw data after the interview has been completed, and the time limitations of doing so. The open-ended nature of our questions will be emphasized in the information and consent sheets. We will also explain the limitations of the researchers' confidentiality, which will be compromised if we are made aware of anyone being subjected to harm and the researcher's duty to report it through the appropriate channels.

2.7 ETHICAL AND REGULATORY CONSIDERATIONS

The quantitative part of this study involves exploratory analysis, machine learning and computer modelling, using anonymised secondary data only. Qualitative work is conducted with physicians who treat stroke patients to enable feedback on exploratory analysis and methods of data visualisation, and to understand attitudes and rationales in regards to thrombolysis in acute stroke care.

All patient data in this study will be from a single source and will be fully anonymised to the researchers: The Sentinel Stroke Audit Programme (SSNAP). No identifiable patient information will be requested or used. Explicit consent for the use of patient identifiable information is not required (although patients can choose to 'opt-out' from SSNAP at individual sites) as the audit has received exemption via section 251 of the NHS Act 2006, and so separate ethical approval for this work is not required. The section 251 approval comes from the Ethics and Confidentiality Committee of the National Information Governance Board (now superseded by the NHS Health Research Authority Confidentiality Advisory Group). The data controller is HQIP, and data access is managed through the HQIP Data Access Request process. The HQIP data access request group meets monthly, with outcomes communicated within 2 weeks of meetings.

For the qualitative interviews with NHS staff we will obtain ethical review and any other regulatory approvals as advised by the sponsor. On receipt of HRA approval, we will seek local site approval through the NHS Capacity & Capability procedures via the HRA Approval process. All study supporting information will be compliant with the General Data Protection Regulations (the GDPR 2018) and the Data Protection Act 2018.

Benefits for clinicians to being a participant in this study is to influence and shape the future of machine learning and use of thrombolysis in stroke care.

We do not see any immediate risks to physicians taking part in the study. In individual interviews the interviewer will ask physicians to explain how they make decisions in regards to thrombolysis. We will not ask about any individual patients and we will not have access to any patient information.

Practitioners working with stroke patients are close to life and death in their daily practice. Being interviewed in detail about their professional practices might bring up upsetting memories of when something did not go to plan. As trained professionals, physicians interviewed are likely to have established ways of dealing with this, and have support within their team to do so. However, the information sheet about the interview will include a reference to this, and emphasise that people can pause or terminate the interview at any time.

The dignity of participants will be upheld by respectful and courteous manners by the researchers before, during and after interviews. The researchers will only ask questions pertinent to the research and as much information as possible will be provided to potential participants in advance of the interview via a neutral point, or if they have already provided consent to be contacted.

Focus groups will be relatively small in size to enable active participation by everyone attending, although the purpose is not to garner a consensus position. The researchers will urge stakeholder participants to uphold confidentiality at all times during the focus group.

Personal contact information for the physicians will be held on a password protected file on the encrypted University of Exeter server. Consent for holding this information will be sought from all participating physicians in advance of the interview. No personal contact information for anyone involved in the study will be held without consent from the individual.

After each interview the audio file will be uploaded onto the encrypted University server. All files will be password protected and only accessible to the research team. As voices are potentially identifiable, audio-files will be deleted once written transcriptions have been received by the researchers.

A key that connects anonymised data to personal information about participating physicians will be stored in a separate file, saved on a password protected secure online version of the One Drive set up specifically for this study, and it will not have a name that identifies it to this

study. The key will enable removal of data after the interview, should interviewees request this.

2.7.1 Assessment and management of risk

As described above we do not expect there to be any serious risks associated with taking part in this study. The three risks identified are:

a) That physicians will become upset when talking about decisions that led to a poor outcome for the patient. This will be highlighted in the information in advance of the interviews, and the researchers will show respect and halt or terminate the interview. We will advise participants that become distressed in any way to seek advice from their manager and will provide a resource list of suitable helplines in the participant information sheet
b) The identification of sub-optimal practice. Where this is identified, we will inform the participant that there is a duty to report sub-optimal practice and that the Study Steering Group will follow a set line of actions, which will be led by the Chief Investigator, should anything require reporting.
c) Lone working risks for the researcher will be by using the University of Exeter Lone Worker Policy and Lone Working Risk Assessment Tool. Risks will be discussed with the Sponsor.

2.7.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, Research Ethics Committee approval will be sought from the Health Research Authority (HRA) Assessment in order to obtain Health Research Authority Approval. Approval at site level will be through the Capacity & Capability process.

Substantial amendments that require review will not be implemented until approval is obtained and any required mechanisms are in place to implement at site.

All correspondence with the relevant Research Ethics Committee will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required.

The Chief Investigator will notify the Research Ethics Committee and the Sponsor of the end of the study.

An annual progress report (APR) will be submitted to the Research Ethics Committee within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the Research Ethics Committee and Sponsor, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Research Ethics Committee and Sponsor.

2.7.3 Regulatory Review & Compliance

Before any site can enrol participants into the study, the Chief Investigator's or designees will ensure that appropriate approvals from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigator's designees, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designees will work with sites (R&D departments at NHS sites as well as the study delivery team) so that the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

2.7.4 Amendments

If the Chief Investigator or Sponsor wishes to make a substantial amendment to the ethics application or the supporting documents, the Chief Investigator will submit a valid notice of amendment to the Research Ethics Committee for consideration, once the Sponsor has signed the amendment. The Research Ethics Committee will provide a response regarding the amendment within 35 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the Research Ethics Committee and Health Research Authority.

Amendments will be notified to the lead NHS R&D office and communicated to the participating organisations (R&D office and local research team) departments of participating sites, to assess whether the amendment affects the NHS permission for that site.

2.7.5 Peer review

This protocol was reviewed by two independent and one internal reviewers:

One external reviewer is a Professor with expertise in Stroke research. Another external reviewer is an Associate Professorial Research Fellow with expertise in research that utilizes quantitative and qualitative methods within one study. The internal reviewer is a Research Fellow with expertise in implementation research and a member of the University of Exeter College for Medicine and Health Research Ethics Committee.

2.7.6 Patient & Public Involvement

- This study is supported by the PenCLAHRC involvement team at the University of Exeter Medical School. The team has a track record of supporting people with complex needs to be research advisors.
- Members of the Peninsula Public Involvement Group, PenPIG, reviewed and informed the development of the research plans and design.

- A patient and carer group of 6-8 people will be formed to help with the analysis of findings, and dissemination of results. This group will meet four times during the course of the study and attend the stakeholder workshop at the end. They will specifically be involved in discussing the research findings from the perspective of patients, considering how the decision-making tool might take patients' views on risk/benefit balance into account, and planning the stakeholder event. A separate meeting with this group will discuss dissemination of the research findings. Patients and carers who are collaborators will be invited to join this group.
- All involved patients and carers will have their travel fully reimbursed and their time recognised with a thank-you payment. Thank-you payments will be higher for patients on the steering committee, in recognition of their longer travel time. We have budgeted for an introductory training course for people new to involvement. Co-applicant Kristin Liabo will provide tailored support in advance of, during and after meetings.
- Governance: One person who cares for her husband that has several health problems after a stroke is involved. She is a collaborator on the study. Her husband has decided that he will contribute knowledge when he feels it is appropriate. The carer representative also cared for her father after he had a stroke. As collaborator the Carer representative will attend quarterly project team meetings. One member of the PPI representation is a stroke survivor who will have a role similar to the Carer representative.

2.7.7 Protocol compliance

This project involves exploratory analysis, machine learning and computer modelling, using anonymised secondary data. Qualitative work is conducted with physicians to enable feedback on exploratory analysis and methods of data visualisation. No patient care is accessed or altered, no patient-identifiable information is used, and no primary data collection from patients is conducted.

The exploratory nature of the quantitative work means that this protocol describes some detail of the analysis, but some of this might change due to interim findings in the data. The Sponsor will be notified of any changes by Mike Allen, researcher and co-investigator.

In regards to the qualitative research, every effort will be made to follow the procedures as described. However, accidental protocol deviations can happen at any time. These will be adequately documented on a form and reported to the chief investigator and the Sponsor by Julia Frost or Kristin Liabo. Where appropriate the HRA Protocol Breach service will be accessed by the Sponsor.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. For this study, this relates to any data release where people's confidentiality is compromised.

2.7.8 Data protection and participant confidentiality

All investigators and study site staff will comply with the requirements of the General Data Protection Regulation 2018 and the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The personal information that will be kept by the study team are participants' contact details and consent forms. Personal contact details will only be kept if participants give direct permission and consent for this. The personal information will be kept on a password protected electronic encrypted file in the study computer folder, on the University's secure server. We will hold no paper copies of personal information. All personal information will be deleted after the study's completion unless otherwise agreed with consent from the participants.

Consent forms will be scanned and stored electronically and in a different folder to the participant data. Audio-files of interviews will be shared with the professional Transcriber via a secure online version of the One Drive specifically for this study, and completed transcripts will be returned securely in the same manner. Once transcripts have been verified and agreed, audio-files will be securely deleted.

All data will be depersonalised/pseudonymised and any identifying information replaced by an unrelated sequence of characters. To allow participants to withdraw from the study, we will hold a linking code between data and personal information but this will be kept separately from any other study information. This is only for the purpose of deleting data should anyone want to withdraw participation. Participants will be informed in advance of the interviews about their rights of access to study information and that after anonymisation, when the data has been analysed and quotes extracted from individual interviews, it may not be possible to fully withdraw all data from all study outputs. For focus groups this will happen shortly after the meetings, due to the group nature of the work and it might not be possible to fully identify the speaker of all data collected.

Data will be maintained in a secure and password protected encrypted computer folder on the University server. The linking code will be kept in a different folder on a different, encrypted computer and filed in a password protected folder, only identifiable to the named qualitative researchers (Julia Frost, Ken Stein and Kristin Liabo). Julia Frost and Kristin Liabo will be responsible for quality control, audit and analysis of data, reporting any problems to chief investigator Ken Stein and the Sponsor.

Personal contact details of participants will not be shared with anyone outside of the agreed research team.

The data will be stored for 10 years. The University of Exeter custodian of the data is the chief investigator, Professor Ken Stein.

2.7.9 Indemnity

Arrangements have been made through the University of Exeter for insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the management/conduct/design of the research.

NHS indemnity scheme will apply for insurance and/or indemnity to meet the potential legal liability of the investigator arising from harm to participants in the conduct of the research.

There are no arrangements in place for payment of compensation in the event of harm to the research participants where no legal liability arises.

2.7.10 Access to the final study dataset

The following individuals will have access to the full quantitative dataset:

- Professor Ken Stein, chief investigator
- Dr Mike Allen, researcher and co-investigator
- Ms Kerry Pearn, researcher and co-investigator
- Mr Andy Salmon, researcher
- Mr Martin James, stroke physician and co-investigator

The following individuals will have access to the full qualitative dataset:

- Professor Ken Stein, chief investigator
- Julia Frost, researcher and co-investigator
- Kristin Liabo, researcher and co-investigator

Because this is not a clinical trial there are not explicit restrictions on access to the full anonymised datasets, but access will be monitored by the individuals named above.

2.8 APPENDICES

2.8.1 Appendix 1 – University of Exeter - Lone worker guideline

POLICY FOR THE SAFE CONDUCT OF FIELD WORK on the SAMueL study

INSTITUTE OF HEALTH SERVICES RESEARCH, UNIVERSITY OF EXETER

This study will involve conducting interviews away from St Luke's Campus. Although almost always conducted without incident, travelling alone to an unfamiliar site can pose risks to the researcher, to confidentiality and may uncover safeguarding risks to patients. **It is ESSENTIAL that you familiarise yourself with this policy and follow it at all times.**

Our research interviews will include audio recordings. The nature of these interviews means that they are highly unlikely to contain identifiable personal information, but it is important to be aware whether they do or not since it is possible that someone mentions a person's name or place of work unintentionally. Audio equipment can be stolen from researchers if left unattended. Such theft risks breaches of confidentiality and the loss of confidence of participants in the study. Similarly, data stolen

may well mean data missing from the research, as participants will rarely consent to repeat interviews. Both are highly undesirable outcomes that we all need to do everything we can to prevent.

Although unlikely, physicians may disclose information that raises safeguarding concerns in regards to poor medical practice; these should be discussed with chief investigator Ken Stein or a nominated deputy **IMMEDIATELY** following the interview, as per the study protocol (insert version number).

Personal safety

1. **A central hard copy log** of all team members' activities will be kept in the main office; **it should be completed by 10am Monday morning every week** and should contain the **names and addresses** of any planned interview trips. Should your schedule change, you should update the diary via the study's administrator Sarah Carter or a colleague if you are not in the office to do so personally. This log will mean that the office will know your movements should you go missing.

2. As we will be conducting field work in several different places, it is useful to send texts around each morning to inform a team member of your whereabouts. This can either be within the study team or the Third Gap team. Team members whose jobs are office-based are only expected to text if they are going to be out of the office. These daily texts help all of us be aware of where colleagues are, and will also highlight if someone goes missing.

3. Before arranging an interview, **carefully review all known details** about the site, including neighbourhood.

4. You should arrange for someone in the study team to be notified of your whereabouts and to be on call should you need to de-brief after the interview.

5. If you are in an interview and feel at all vulnerable, your safety is your priority; **abandon the interview politely and leave**.

Audio recordings of interviews

6. **Our overarching principle in handling data is that all data (audio or paper) is to be filed in the office AS SOON AS POSSIBLE and preferably immediately** with identifiable details stripped away.

7. **NEVER leave portable equipment and / or paper records unattended** when out of the office. Lock everything away in the boot of your car or keep it near you and visible when on assessment visits. Keep equipment and paper records securely locked away if you are unable to return them to the office on the day an assessment is completed and return them for fling as soon as possible.

8. All data gathered using audio recordings is to be downloaded from portable equipments **AS SOON AS POSSIBLE and preferably immediately** after the interview onto an encrypted storage drive (NOT a lap top) or the Cloud.

9. Researchers are expected to attend the office **AT LEAST ONCE A WEEK** to download **ALL** the data collected that within the last working week.

2.8.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Details of all protocol amendments will be listed here whenever a new version of the protocol is produced.

Protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC.

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. *The Lancet* 2014;383(9913):245-55. doi: https://doi.org/10.1016/S0140-6736(13)61953-4
2. Sentinel Stroke National Audit Programme. Annual Results Portfolio April 2015 March 2016. SSNAP, 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. *The Lancet* 2015;386(10010):2257-74. doi: https://doi.org/10.1016/S0140-6736(15)00195-6
4. 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. *The Lancet* 2014;384(9958):1929-35. doi: https://doi.org/10.1016/S0140-6736(14)60584-5
5. Meretoja A, Keshtkaran M, Saver JL, et al. Stroke thrombolysis: Save a minute, save a day. *Stroke* 2014;45(4):1053-8. doi: https://doi.org/10.1161/STROKEAHA.113.002910
6. Saver JL. Time is brain - Quantified. *Stroke* 2006;37(1):263-6.
7. Lyden P. Thrombolytic therapy for acute stroke - not a moment to lose. *New England Journal of Medicine* 2008;359(12):1393-5.
8. Eissa A, Krass I, Bajorek BV. Barriers to the utilization of thrombolysis for acute ischaemic stroke. *Journal of clinical pharmacy and therapeutics* 2012;37(4):399-409. doi: https://doi.org/10.1111/j.1365-2710.2011.01329.x
9. Carter-Jones CR. Stroke thrombolysis: barriers to implementation. *International Emergency Nursing* 2011;19(1):53-7. doi: https://doi.org/10.1016/j.ienj.2010.02.005
10. Engelter ST, Gostynski M, Pap S, et al. Barriers to stroke thrombolysis in a geographically defined population. *Cerebrovascular Diseases* 2007;23(2-3):211-15. doi: https://doi.org/10.1159/000097643
11. De Brun A, Flynn D, Ternent L, et al. Factors that influence clinicians' decisions to offer intravenous alteplase in acute ischemic stroke patients with uncertain treatment indication: results of a discrete choice experiment. *International Journal of Stroke* 2018;13(1):74-82. doi: https://doi.org/10.1177/1747493017690755
12. Thompson R, De Brun A, Flynn D, et al. Factors that influence variation in clinical decision-making about thrombolysis in the treatment of acute ischaemic stroke: results of a discrete choice experiment. *Health Services and Delivery Research* 2017;5(4) doi: DOI: 10.3310/hsdr05040

13. McCormick MT, Reeves I, Baird T, et al. Implementation of a stroke thrombolysis service within a tertiary neurosciences centre in the United Kingdom. *QJM: An International Journal of Medicine* 2008;101(4):291-8. doi: https://doi.org/10.1093/qjmed/hcn002
14. Lahr MMH, Luijckx GJ, Vroomen PCAJ, et al. The chain of care enabling tPA treatment in acute ischemic stroke: a comprehensive review of organisational models. *Journal of Neurology* 2013;260(4):960-8.
15. Lahr MMH, Van Der Zee DJ, Luijckx GJ, et al. A simulation-based approach for improving utilization of thrombolysis in acute brain infarction. *Medical Care* 2013;51(12):1101-5.
16. Monks T, Pitt M, Stein K, et al. Maximizing the population benefit from thrombolysis in acute ischemic stroke: A modelling study of in-hospital delays. *Stroke* 2012;43(10):2706-11.
17. Monks T, Pitt M, Stein K, et al. Hyperacture stroke care and NHS England's business plan. *BMJ* 2014;348(May):g3049.
18. Kotsianis SB, Zaharakis I, Pintelas P. Supervised machine learning: a review of classification techniques. *Informatica* 2007;31:249-68. doi: https://doi.org/10.1111/j.1747-4949.2010.00479.x
19. Pope C, Mays N. Qualitative research in health care. Oxford: Blackwell 2006.
20. Green J, Thorogood N. Qualitative methods in health research. London: Sage 2004.
21. Bembenek J, Kobayashi A, Sandercock P, et al. How many patients might recieve thrombolytic therapy in the light of the ECASS-3 and IST-3 data? *International Journal of Stroke* 2010;5(5):430-31. doi: https://doi.org/10.1111/j.1747-4949.2010.00479.x
22. Whiteley W, Emberson J, Lees KR, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. *The Lancet Neurology* 2016;15(9):925-33. doi: https://doi.org/10.1016/S1474-4422(16)30076-X
23. 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: https://doi.org/10.1136/bmj.g4757
24. Miles MB, Huberman AM. Qualitative data analysis. Thousand Oaks: Sage 1994.
25. Healthcare Quality Improvement Partnership. Rising to the challenge: the fourth SSNAP annual report. 2017
26. Frost J, Garside R, Cooper C, et al. A qualitative synthesis of diabetes self-management strategies for long term medical outcomes and quality of life in the UK. *BMC Health Services Research* 2014;14:348. doi: 10.1186/1472-6963-14-348
27. Raynor DKT, Blenkinsopp A, Knapp P, et al. A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines *Health Technology Assessment* 2007;11(5):1-178.