Paramedic identification of stroke mimic presentations: development and preliminary evaluation of a pre-hospital clinical assessment tool

A thesis submitted for the degree of Doctor of Philosophy

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Abstract

Background

Stroke mimic (SM) conditions produce stroke-like symptoms through diverse mechanisms. Up to 43% of pre-hospital suspected stroke patients are SM because identification tools prioritise sensitivity over specificity, leading to inefficient use of ambulances and stroke services. No existing pre-hospital SM identification tools could be identified. A pragmatic SM identification tool using easily available information from suspected stroke patients was developed.

Methods

A systematic literature review and a national paramedic survey generated possible tool content. Independent predictors were isolated by regression analysis of selected variables documented in ambulance records of suspected stroke patients linked to primary hospital diagnoses (derivation dataset, n=1,650, 40% SM). The tool was refined using an expanded dataset (n=3,797, 41% SM), usability testing and professional focus groups. The potential clinical impact was evaluated through basic service efficiency modelling and focus groups.

Results

The "STEAM tool" combines six variables:

- 1 point for **S**ystolic blood pressure<90mmHg
- 1 point for **T**emperature>38.5^{o}C with heart rate>90bpm
- 1 point for seizures or 2 points for seizures with known diagnosis of **E**pilepsy
- 1 point for **A**ge<40 years or 2 points for age<30 years
- 1 point for headache with known diagnosis of **M**igraine
- 1 point for FAST-ve suspected stroke

A score of ≥2 on STEAM predicted SM diagnosis in the refinement dataset with 5.5% sensitivity, 99.6% specificity and positive predictive value (PPV) of 91.4%. External validation (n=1,848, 33% SM) showed 5.6% sensitivity, 99.5% specificity and a PPV of 85.0%.

Focus groups with paramedics and hospital clinicians identified benefits and risks to patients

and clinical services from using STEAM.

Conclusions

A multi-method approach developed and validated a tool using common clinical characteristics to identify a small proportion of SM patients with a high degree of certainty. The tool appears feasible for pre-hospital use but its impact will depend upon local models of stroke care.

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Thesis author responsibilities / contribution

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Publications, posters and presentations

Publications

McClelland, G., Rodgers, H., Flynn, D., Price, C. (2018). The frequency, characteristics and aetiology of stroke mimic presentations: a narrative review. *European Journal of Emergency Medicine*. Published online 1st May 2018. doi: 10.1097/MEJ.0000000000000550

McClelland, G., Rodgers, H., Flynn, D., Price, C. (2018). Development and validation of a pragmatic pre-hospital tool to identify stroke mimic patients (poster abstract). *BMJ Open*, 8(Suppl 1).

McClelland, G., Flynn, D., Rodgers, H., Price, C. (2017). Development of a pre-hospital stroke mimic identification tool: a focus group study with healthcare professionals (poster abstract). *International Journal of Stroke,* 12(5S), pp. 22.

McClelland, G., Rodgers, H., Flynn, D., Price, C. (2017). Development of a pre-hospital assessment to identify stroke mimic conditions (poster abstract). *EMJ,* 34(10), pp. 14.

McClelland, G., Flynn, D., Rodgers, H., Price, C. (2017). A survey of UK paramedics' views about their stroke training, current practice and the identification of stroke mimics. *British Paramedic Journal,* 2(1), pp. 4–15.

McClelland, G., Rodgers, H., Flynn, D., Price, C. (2016). The frequency and diagnosis of stroke mimics in pre-hospital and hospital studies: a systematic literature review (poster abstract). *International Journal of Stroke*, 11(4S), pp 30-31.

McClelland, G., Flynn, D., Rodgers, H., Price, C. (2015). A systematic review of the clinical and demographic characteristics of adult patients with stroke mimics. PROSPERO: CRD42015026457. Available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026457 [Accessed 21/06/18].

Posters

Title: When is a stroke not a stroke? Development and validation of a pragmatic pre-hospital tool to identify stroke mimic patients
Conference: EMS2018
Location: Copenhagen, Denmark
Date: 16-18th April 2018

Title: Development of a pre-hospital stroke mimic identification tool: a focus group study with healthcare professionals
Conference: The UK Stroke Forum
Location: Liverpool, UK
Date: 28-30th November 2017

Title: When is a stroke not a stroke? Development of the STEAM tool to identify pre-hospital stroke mimics (Best poster prize)
Conference: North East and North Cumbria Clinical Research Network Building our Research Capacity and Capability
Location: Newcastle-upon-Tyne, UK
Date: 7th November 2017

Title: When is a stroke not a stroke? Development of the STEAM tool to identify pre-hospital stroke mimics
Conference: Newcastle University Cardiovascular Research Centre trainees conference
Location: Newcastle-upon-Tyne, UK
Date: 28th June 2017

Title: When is a stroke not a stroke? Development of the STEAM tool to identify pre-hospital stroke mimics
Conference: EMS999 Research Forum
Location: Bristol, UK

Date: 28-29th March 2017

Title: The frequency and aetiology of stroke mimics: a systematic literature review

Conference: The UK Stroke Forum

Location: Liverpool, UK

Date: 28-30th November 2016

Title: The frequency and aetiology of stroke mimics: a systematic literature review

Conference: North East Postgraduate Conference

Location: Newcastle-upon Tyne, UK

Date: 24-25th November 2016

Title: The frequency and aetiology of stroke mimics: a systematic literature review

Conference: Newcastle University Cardiovascular Research Centre trainees conference

Location: Newcastle University, UK

Date: 14th September 2016

Presentations

Title: Why pre-hospital stroke care need to change

Conference: EMS2018

Location: Copenhagen, Denmark

Date: 16-18th April 2018

Title: Can we improve stroke care by identifying stroke mimics? (Highest quality research prize)

Conference: EMS999 Research Forum

Location: Stirling, UK

Date: 26-27th March 2018

Title: Improving pre-hospital stroke identification by reducing mimics

Conference: Northern Emergency Medicine Conference

Location: Durham, UK

Date: 9th January 2018

Title: But is it a mimic? (part of stroke identification workshop)

Conference: The UK Stroke Forum

Location: Liverpool, UK

Date: 28-30th November 2017

Title: When is a stroke not a stroke? Development of a pre-hospital stroke mimic identification tool

Conference: Webinar for College of Paramedics Research and Development Committee

Location: Webinar

Date: 18th October 2017

Title: When is a stroke not a stroke?

Conference: North West Stroke CPD Event

Location: Salford, UK

Date: 3rd August 2017

Title: Paramedic Stroke Mimic Project

Conference: North East Stroke Patient and Carer panel

Location: Washington, UK

Date: 27th April 2017

Title: When is a stroke not a stroke?

Conference: Institute of Neuroscience 2nd year postgraduate symposium

Location: Newcastle-upon-Tyne, UK

Date: 26th April 2017

Title: Paramedic Stroke Mimic Project

Conference: Stroke Research Group presentation day

Location: Newcastle-upon-Tyne, UK

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Title: Pre-hospital research and the Paramedic Stroke Mimic Project

Conference: Explore lifelong learning event

Location: Newcastle-upon-Tyne

Date: 1st March 2017

Title: Paramedic Stroke Mimic Project

Conference: Regional Stroke Advisory Group meeting

Location: Durham, UK

Date: 10th January 2017

Title: Paramedic Stroke Mimic Project

Conference: North East Ambulance Service Clinical Effectiveness Group

Location: Newcastle-upon-Tyne, UK

Date: 8th December 2016

Title: Development of a pre-hospital assessment to identify stroke mimic conditions

Conference: Council for Allied Health Professionals Research Best Practice in AHP Research event

Location: Newcastle-upon-Tyne, UK

Date: 5th December 2016

Title: The frequency and diagnoses of stroke mimics

Conference: North East Postgraduate Conference

Location: Newcastle-upon-Tyne, UK

Date: 24-25th November 2016

Title: Identification of pre-hospital stroke mimics

Conference: CRN Regional Stroke Specialty Research Update meeting

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Title: Identification of pre-hospital stroke mimics

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List of abbreviations

AF	Atrial Fibrillation
BM	Boehringer Mannheim (blood sugar)
CCS	Clinical Classifications Software
CHF	Congestive Heart Failure
COP	College of Paramedics
CT	Computerised Tomography
DTN	Door to Needle time
ECCM	Emergency Care Clinical Manager
ED	Emergency Department
EMS	Emergency Medical Services
EPCR	Electronic Patient Care Record
EPRF	Electronic Patient Report Form
FAST	Face, Arms, Speech Test
GCS	Glasgow Coma Scale
HASU	Hyper-Acute Stroke Unit
HES	Hospital Episode Statistics
HR	Heart Rate
ICD	International Classification of Diseases
LOS	Length of Stay
MI	Myocardial Infarction
NEAS	North East Ambulance Service NHS Foundation Trust
NHCT	Northumbria Healthcare NHS Foundation Trust
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NWAS	North West Ambulance Service NHS Trust
PMH	Past Medical History
PPV	Positive Predictive Value
RCP	Royal College of Physicians
RCT	Randomised Controlled Trial
ROC	Receiver Operating Characteristic

RR	Respiratory Rate
SaO2	Peripheral Oxygen Saturation
SBP	Systolic Blood Pressure
SM	Stroke Mimic
SRFT	Salford Royal NHS Foundation Trust
SSNAP	Sentinel Stroke National Audit Programme
STEMI	ST segment Elevation Myocardial Infarction
TIA	Transient Ischaemic Attack

Chapter 1.0 Overview

1.0.1 Overview

Stroke is a serious medical emergency caused by disruption in the blood flow to brain tissue by either a blockage (ischaemic stroke) or a bleed (haemorrhagic stroke). Over 80,000 people each year are hospitalised with stroke and it is the fourth commonest cause of death in the UK (RCP, 2016; The Stroke Association, 2018). Despite falling incidence of stroke in the developed world the global incidence of stroke is increasing (Feigin *et al.*, 2009). Stroke is one of a small number of time critical conditions dealt with by pre-hospital emergency medical services (EMS) due to the short treatment window and accounts for around 2% of emergency calls (Seymour *et al.*, 2012).

Stroke mimics (SM) are conditions which produce the same symptoms as stroke but do not have a cerebrovascular aetiology. SM are common in all clinical settings due to the wide variety of clinical stroke presentations and alternative aetiologies but are particularly common in pre-hospital care, partly driven by the operational performance of stroke recognition instruments (Rudd *et al.*, 2016a). This thesis focusses on pre-hospital stroke care which is mainly provided by paramedics working within ambulance services in the UK. Paramedic will be used throughout this thesis as a term to encompass all pre-hospital care providers unless otherwise stated.

This project aimed to develop a novel SM identification tool and demonstrate whether it is feasible and acceptable to integrate this into the pre-hospital assessment of patients following initial recognition of suspected stroke. Early identification of a patient as a SM rather than a stroke may change the initial hospital that the patient is transported to and the focus of their immediate assessment and care.

Sequential diagnosis is a recognised approach in healthcare where a simple initial test is used which is sensitive to the condition under examination, and then the diagnosis is refined with a second test (Denny *et al.*, 2000; Iwasaki *et al.*, 2003; Abdul-Ghani *et al.*, 2011). The concept is that the two tests performed sequentially have a better combined performance than either test in isolation. In UK practice the SM tool would be primarily used in sequence with the Face Arms Speech Tool (FAST) (Harbison *et al.*, 2003).

The purpose of developing the SM tool was to improve the overall accuracy of pre-hospital stroke diagnosis by reducing the number of SM incorrectly labelled as possible stroke. Application of the SM identification tool was not explored outside of pre-hospital care and there was no attempt to improve the initial identification of stroke.

Previous research in pre-hospital stroke care has reported a range of SM rates from 4-62% (Saver *et al.*, 2015; Andsberg *et al.*, 2017). Increasing the precision of stroke identification by paramedics could improve future pre-hospital stroke research through more efficient delivery, more realistic sample size calculations and analysis which more accurately reflects clinical service activity (Libman *et al.*, 1995; Restrepo *et al.*, 2010).

If identification of SM in the pre-hospital setting is possible, using data easily available to paramedics, then it may be possible to direct SM patients along more appropriate care pathways. A simple example of how a SM tool could modify the current pathway of care is shown in figure 1.0.1.

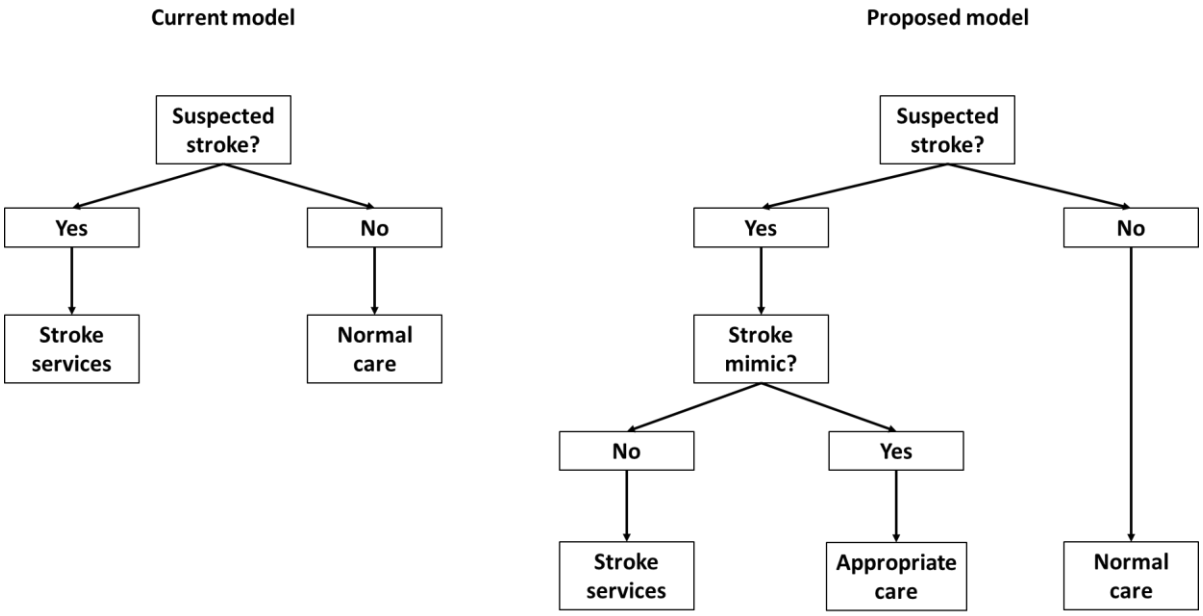


Figure 1.0.1 Simple model of SM tool added to current stroke care pathway

SM identification could be beneficial for the patient, the ambulance service and stroke services depending on how well the SM identification tool performs. Patients would be taken to the most appropriate location for their condition, the ambulance service would avoid unnecessary bypass of local hospitals and secondary repatriation journeys and stroke services would reduce the number of SM patients admitted which reduces demand on their services.

1.0.2 Project aims

The aim of the work contained within this thesis was to develop and evaluate a pre-hospital SM identification tool based on information commonly collected during paramedic assessment in order to enable easy implementation. This consisted of four more specific aims:

- A1. A systematic review to summarise the frequency, underlying aetiology and common characteristics of SM.
- A2. Analysis of pre-hospital data to develop, refine and validate a SM identification tool for use in the pre-hospital setting.
- A3. Qualitative exploration of the acceptability and implications of pre-hospital SM identification with clinicians.
- A4. Basic modelling of the service level impact resulting from the introduction of a SM identification tool.

1.0.3 Research design

Multiple methods were used during the SM identification tool development, refinement and validation. Multiple, or mixed, methods are often used in pre-hospital research as a pragmatic way to address the complex environment (McManamny *et al.*, 2014).

The tool development was underpinned by the creation of a pre-hospital dataset linked to hospital based patient diagnoses. This was analysed to identify clinical characteristics documented by paramedics which differentiated statistically between stroke and SM. These characteristics were placed in the context of the findings of a systematic literature review, the results of a survey of UK paramedics and clinical input from the study team to develop the first iteration of the SM tool.

Focus groups and semi-structured interviews collected views from healthcare professionals involved in stroke care including paramedics, doctors and nurses. Thematic analysis informed further development of the SM tool, described paramedic's views about the usability of the initial tool in practice and reported healthcare professional's opinions about the overall service impact.

Prospective application of the tool by National Health Service (NHS) paramedics in pre-hospital practice provided further data on acceptability, barriers and facilitators to clinical

deployment. Basic modelling explored the potential impact of introduction of a SM tool into clinical practice.

The overall research process fits within the 'development' section of the Medical Research Council's (MRC) framework for complex intervention development (Craig *et al.*, 2008).

1.0.4 Structure of thesis

This thesis is presented in four parts. Part one describes the background to the study, the literature describing SM and the development of the initial SM tool. Part two describes the usability testing and refinement of the initial SM tool. The third part includes validation of the SM tool, basic modelling work exploring the potential impact of introducing a SM tool and clinicians' views on the final SM tool. The fourth part of the thesis discusses the findings of the whole project. The chapters of the thesis are summarised below and the overall structure is displayed in figure 1.0.2.

- Part 1
    - Chapter 1.1 presents the clinical context for this thesis and explores how diagnostic tools are described.
    - Key literature about SM are synthesised and discussed in chapter 1.2. This describes the variation in SM definitions, the reported rates of SM and how the rates of SM differ across healthcare settings.
    - Views about SM from a sample of paramedics across the UK, and other aspects of their practice related to stroke, are reported in chapter 1.3.
    - Data and methods involved in the development of the initial SM tool are described in chapters 1.4 and 1.5.
- Part 2
    - Thematic analysis of views from focus groups with paramedics and hospital clinicians about the initial SM tool is reported in chapter 2.1.
    - Chapter 2.2 reports the refinement of the initial SM tool using additional linked clinical datasets.
    - Experiences of paramedics involved in prospective usability testing of the initial SM tool are described in chapter 2.3.

- Part 3
    - Validation of the refined SM tool in a separate clinical dataset is described in chapter 3.1.
    - Basic modelling of the service level impact of a SM tool is reported in chapter 3.2.
    - Chapter 3.3 describes thematic analysis of focus groups with pre-hospital and hospital clinicians exploring the refined and validated SM tool.
- Part 4
    - Chapter 4.0 discusses and summarises the whole project.

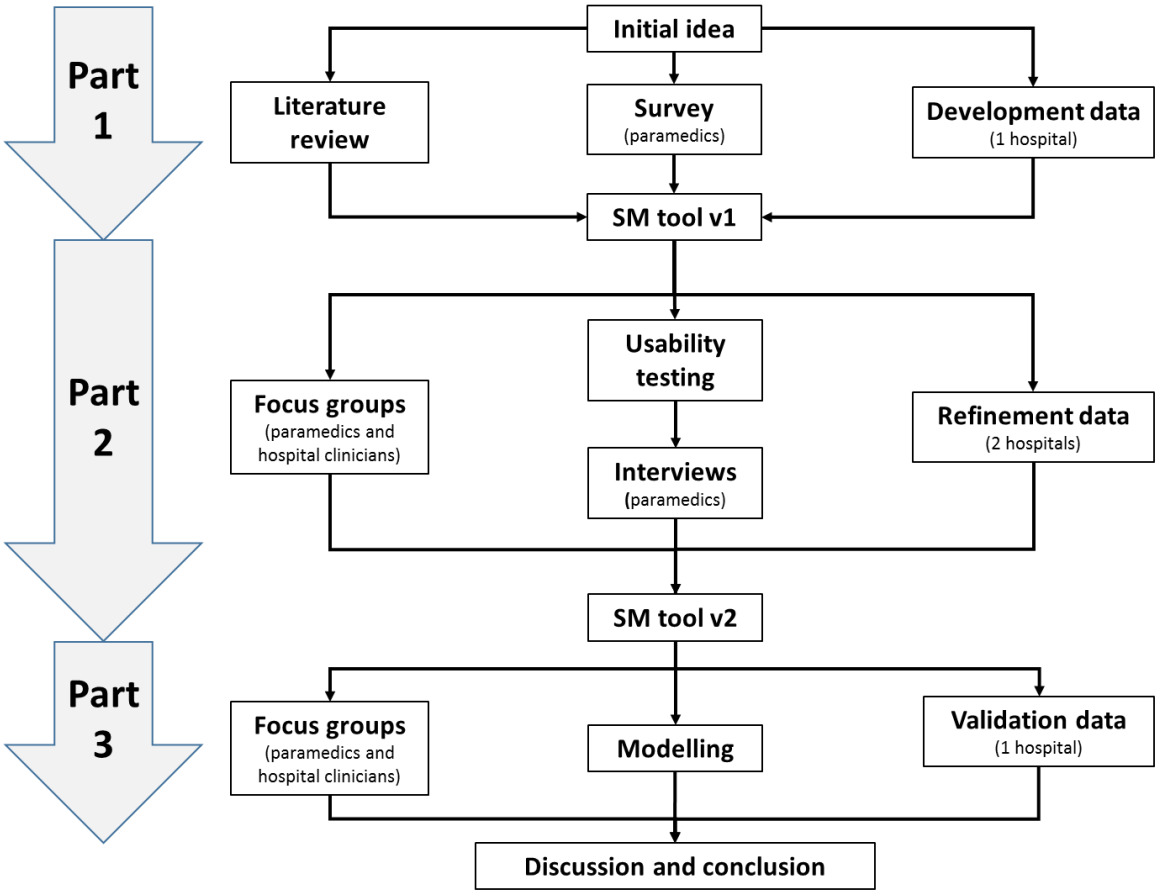


Figure 1.0.2 Flowchart with overview of pre-hospital SM project

1.0.5 Summary

This chapter has given a brief overview of the thesis content. The next chapter expands upon pre-hospital stroke identification, defines the terminology that will be used to discuss stroke diagnosis and shows how this work differs from existing SM identification tools.

Chapter 1.1 Background and rationale

1.1.1 Introduction

This chapter will briefly describe the clinical context of emergency stroke care and how the pre-hospital and hospital phases combine to identify patients for administration of emergency treatments. Most pre-hospital stroke identification tools, such as FAST, are designed to identify the maximum number of stroke patients using symptoms alone, as opposed to hospital practice where symptoms are considered in conjunction with neuroimaging. Consequently most pre-hospital tools have poor specificity and identify a large number of "false positive" SM patients.

1.1.2 Chapter aims and objectives

The aim of this chapter is to provide the background, clinical context and methodological rationale for the development of a SM identification tool.

The objectives of this chapter are:

- Summarise stroke as a condition.
- Describe the current UK model of pre-hospital and acute hospital stroke care.
- Describe how the performance of diagnostic tests are assessed and compared.
- Describe existing SM identification tools and justify the need for a pre-hospital SM tool.

1.1.3 Overview of stroke

The World Health Organisation (WHO) described stroke as "*a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin*" (Hatano, 1976).

There are two types of stroke aetiology: haemorrhagic and ischaemic. In simple terms, haemorrhagic stroke is caused by a bleed within the brain whereas ischaemic stroke is caused by a clot, or thrombus, occluding a blood vessel within the brain. Ischaemic stroke is more common accounting for around 85% of stroke. Clinical presentations from stroke produce symptoms according to the location, size and duration of the cerebral insult. Short

episodes result in Transient Ischaemic Attacks (TIAs) which by definition must completely resolve within 24 hours with no lasting effect. TIAs can be precursors to stroke (Amarenco *et al.*, 2016).

For many years acute stroke was considered to be untreatable. The development of brain imaging in the form of Computed Tomography (CT) in the 1970s and the trials of drugs which could dissolve the occluding thrombus (thrombolytics) causing ischaemic stroke in the 1990s radically changed stroke care provision and outcomes (Snow, 2013).

1.1.4 Emergency stroke treatment

The current model of acute stroke care in the UK focusses on rapid identification of suspected stroke patients, access to specialist stroke units and delivery of reperfusion treatment (thrombolysis and/or thrombectomy) for eligible ischaemic stroke patients. Rapid identification of stroke is vital as the effectiveness of thrombolysis is time dependent. A Cochrane review of thrombolysis for acute ischaemic stroke (Wardlaw *et al.*, 2014) reported that thrombolysis with alteplase had a net benefit in terms of reducing death and disability up to 3 hours from symptom onset (OR 0.7, 95% CI 0.5 to 0.8, P<0.0001; 6 trials, 1,779 participants) and was potentially beneficial up to 6 hours from onset (OR 0.8, 95% CI 0.8 to 0.9, P=0.0006; 8 trials, 6,729 participants). The current time window for thrombolysis is 4.5 hours from stroke onset as past this point the risks outweigh the benefits (Emberson *et al.*, 2014). Very recent studies are exploring whether this treatment window can be extended for carefully selected patients (Ma *et al.*, 2018; Thomalla *et al.*, 2018).

Mechanical thrombectomy (Evans *et al.*, 2017) is a newer treatment for ischaemic stroke which involves physically removing the occluding thrombus if it is within the larger cerebral blood vessels. The HERMES collaboration reported a meta-analysis of five recent thrombectomy trials (Goyal *et al.*, 2016a) which demonstrated benefit based on modern techniques, devices and highly specialised services. Mechanical thrombectomy has a slightly longer treatment window than thrombolysis, around 6 hours although recent trials show it may be longer (Nogueira *et al.*, 2018), and is effective (number needed to treat (NNT) of 2.6 to reduce disability) for patients with large vessel occlusions (LVO) which can be severely disabling. Thrombectomy was provisionally commissioned by the NHS in early 2017 but in 2018 was not widely available (NHS England, 2017). The need to identify patients for this treatment at the earliest opportunity has led to the development of pre-hospital stroke tools

focused on identifying patients with symptoms associated with LVO (Perez de la Ossa *et al.*, 2014; Purrucker *et al.*, 2017). These are not in current use in the UK due to the limited availability of thrombectomy and uncertainty over the best model for accessing these services (Evans *et al.*, 2017; Milne *et al.*, 2017).

The Keogh Urgent and Emergency Care Review (UEC Review Team and ECIST, 2015) (p11) highlighted acute stroke as a key condition which would benefit from service centralisation. Delivering stroke care at specialist multi-disciplinary units has been shown to reduce both death and dependency (Stroke Unit Trialists Collaboration, 2013). Specialist stroke units covering large geographical areas with high numbers of patients, known as Hyper-Acute Stroke Units (HASUs), have been shown to be an effective method of delivering high quality, evidence based interventions and care in the first 48-72 hours (McMeekin *et al.*, 2013; Morris *et al.*, 2014; Ramsay *et al.*, 2015).

Stroke care is moving in a similar direction to other conditions that have been centralised e.g. trauma and cardiac emergencies. However, stroke care differs from trauma and cardiac care as initiation of the stroke care pathway is more challenging due to the lack of an objective diagnostic test and the frequency and number of SM conditions.

The centralisation of stroke care at a small number of hospitals has required ambulance services to adapt and develop pathways for stroke patients to access these specialist centres. These pathways rely on pre-hospital identification, using tools like FAST, of patients who may be eligible for thrombolysis or who would benefit from HASU care. Further centralisation of specialist stroke services is likely to be seen in the future as thrombectomy services are developed.

The short treatment window for reperfusion therapies, combined with the benefits of early access to specialist stroke services, means that early stroke recognition is very important for improving patient outcomes and reducing economic impact. Paramedics are often the first healthcare professionals to assess an acute stroke patient. The accuracy of paramedic's recognition of stroke is important as their decision about which is the most appropriate hospital for the patient influences the timeliness of the patient's access to specialist stroke care and potential treatments.

1.1.5 Pre-hospital stroke care

For the purpose of this work, pre-hospital care is used to refer to emergency or unscheduled pre-hospital care. In the UK pre-hospital care is mainly provided by NHS ambulance paramedics on a regional basis. This definition excludes physician led primary care (General Practice (GP)) or nurse led routine out of hospital care (district nurses etc.) although the results of this work could be of interest to these groups as well.

Pre-hospital care is evolving rapidly but pre-hospital stroke care has remained largely unchanged for many years. Improving pre-hospital clinical care pathways for stroke patients has been identified as a national priority by the National Ambulance Service Medical Directors (National Ambulance Service Medical Directors, 2014).

Paramedics provide the first direct healthcare contact for around two thirds of stroke patients admitted to hospital (Bayer *et al.*, 2013). Pre-hospital care of stroke patients focusses upon identification of the patient as a suspected stroke and rapid transport to an appropriate destination with a pre-notification which allows the receiving unit to prepare for the patients' arrival. Pre-notification by paramedics has been shown to be associated with improvements in time to treatment for stroke patients (McKinney *et al.*, 2013; Oostema *et al.*, 2014; Sheppard *et al.*, 2015b).

National guidelines recommend pre-hospital stroke identification using a standardised assessment process, such as FAST, but due to the possibility of missed cases, paramedics are also encouraged to make a provisional diagnosis based upon their own clinical judgement (Intercollegiate Stroke Working Party, 2016).

1.1.6 Pre-hospital stroke identification tools

There are a range of tools designed to help with pre-hospital stroke identification. The majority of UK paramedics use the FAST (Harbison *et al.*, 2003). This was developed within the North East of England as a rapid and simple stroke identification tool for use by paramedics based upon a review of North American stroke identification tools. This followed research into paramedic triage of stroke patients within Newcastle upon Tyne and the establishment of a rapid ambulance protocol allowing transport of suspected stroke patients directly to stroke services. This was originally necessary as the stroke services were in a different hospital to the emergency department (ED) (Harbison *et al.*, 1999).

In order to be sensitive to different possible combinations of symptoms across a broad range of patients, all identification instruments overestimate stroke incidence and result in SM being identified as stroke (Rudd *et al.*, 2016a). A summary of common pre-hospital stroke identification tools is shown in table 1.1.1 (Adapted from Rudd *et al.,* 2016a). Sensitivity, specificity and positive predictive value (PPV) are explained in the next section.

Pre-hospital stroke identification instruments with greater precision than FAST are described, but these were designed to focus on stroke patients potentially suitable for thrombolysis by excluding patients based on age or disability criteria (e.g. LAPSS and MASS). Other tools have been developed in hospital but have not shown additional value when applied in the pre-hospital setting (e.g. Recognition Of Stroke In the Emergency Room (ROSIER) (Fothergill *et al.*, 2013)).

The low specificity of pre-hospital stroke identification tools results in patients being taken to specialist stroke services despite 25-50% of pre-hospital suspected strokes receiving a SM final diagnosis.

Table 1.1.1 Summary of common pre-hospital stroke identification instruments (Adapted from Rudd et al (2016))										
	Instrument criteria						**Performance**			
Instrument	**Face**	**Arms**	**Grip**	**Speech**	**Leg**	**Vision**	**Sensitivity**	**Specificity**	**PPV**	**Notes**
Cincinnati Prehospital Stroke Scale (CPSS)	Yes	Yes	No	Yes	No	No	44-95	24-79	40-88	None
Face Arms Speech Test (FAST)	Yes	Yes	No	Yes	No	No	79-97	13-88	62-89	GCS<7 or head injury exclusions in original paper
Los Angeles Prehospital Stroke Scale (LAPSS)	Yes	Yes	Yes	No	No	No	59-91	48-97	73-98	Inclusions: age>45, no seizures, symptoms<24 hours, not wheelchair bound or bedridden,
Medic Prehospital Assessment for Code Stroke	Yes	Yes	No	Yes	Yes	Yes	74	33	47	Inclusions: no seizures, symptoms<24 hours, BM within normal limits
Melbourne Ambulance Stroke Scale (MASS)	Yes	Yes	Yes	Yes	No	No	83-90	74-85	64-90	Inclusions: age>45, no seizures, symptoms<24 hours, not wheelchair bound or bedridden,
Ontario Prehospital Stroke Screening Tool	Yes	Yes	No	Yes	Yes	No	89	80	90	Exclusions: uncorrected ABC problems, hypoglycaemia, seizures, GCS<10, terminal

1.1.7 Assessment of diagnostic tests

This project focusses on the diagnosis of SM conditions, so it is important to define the terms that are used to describe and compare diagnostic tests.

Measures of diagnostic performance are normally calculated by using a 2x2 table comparing the test in question against a gold standard or reference test. An example of this is shown in table 1.1.2. The definitions below are taken from chapter 38, Diagnostic tools, (Petrie and Sabin, 2009).

Table 1.1.2 2x2 table showing diagnostic test performance

		Gold standard test		
		Disease present	**Disease absent**	**Total**
Test under investigation	**Positive test**	A	B	A+B
	Negative test	C	D	C+D
	Total	A+C	B+D	A+B+C+D

The outputs from this 2x2 table allow the performance of the diagnostic test to be calculated. The commonly used terms are described below:

- Sensitivity – proportion of individuals with a disease who are correctly identified by a test = A/(A+C)
- Specificity – proportion of individuals without a disease who are correctly identified by a test = D/(B+D)
- Positive predictive value (PPV) – proportion of individuals with a positive test result who have the disease = A/(A+B)
- Negative predictive value (NPV) – proportion of individuals with a negative test result who do not have the disease = D/(C+D)

The results of a diagnostic test are also referred to as:

- True positive – the test correctly identifies the presence of the disease = A
- True negative – the test correctly identifies the absence of the disease = D
- False positive – the test incorrectly identifies the presence of the disease = B
- False negative – the test incorrectly identifies the absence of the disease = C

In terms of stroke diagnosis a true positive is a stroke; a false positive is a SM; a false negative is known as a stroke chameleon (i.e. a stroke misdiagnosed as another condition) and a true negative is where stroke was correctly not one of the diagnoses under consideration. True negatives are not reported as they constitute all other activity within an ambulance service context.

The positive and negative likelihood ratios for a diagnostic test can also be reported (Grimes and Schulz, 2005). The positive likelihood ratio (LR+) is the ratio of true positives to false positives. If in a population of 50 patients with the condition and 50 patients without the conditions, 40 patients with the condition would have a true positive results and 10 patients without would have a false positive result then the LR+ is (40/50)/(10/50) = 0.8/0.2 = 4. This can be interpreted as patients with the condition are 4 times more likely to get a positive test result than patients without. The negative likelihood ratio (LR-) is the opposite of this and is the ratio of false negatives to true negatives. This can be interpreted as how likely a negative result is in a patient without the condition which in the same population would be 0.25. Likelihood ratios measure from 0 to infinity. A likelihood ratio of 1 means the test does not differentiate between patients with or without the condition, whereas the further the likelihood ratio is from 1 the greater the value of the test.

Receiver Operating Characteristic (ROC) curves are a graphical format for displaying the performance of a test by plotting sensitivity against one minus specificity for various test values. This produces a curve on a chart that can be used to determine the value of the test and the optimum cut-off point for the test. Example ROC curves are shown in figure 1.1.2.

A ROC curve can be examined to determine the Area Under the Curve (AUC). AUC is a method of measuring the tests value at discriminating the condition of interest. AUC is measured from 0 to 1. AUC of 0 represents the test being completely wrong, AUC of 0.5 means the test performs no better than chance and AUC of 1 represents perfect discrimination (Hajian-Tilaki, 2013; Hoo *et al.*, 2017). In practice the further the ROC curve is towards the upper left of the graph the better the test performs. The AUC for the tests shown in figure 1.1.2 are shown in table 1.1.3. Figure 1.1.2 and table 1.1.3 taken from (Zhao *et al.*, 2016).

Table 1.1.3 Area under the ROC curve (AUC) of five stroke predictor variables			
Predictor variables	**AUC (mean ± SE)**	**p**	**95% CI**
VI value	0.844 ± 0.041	0.000	0.764–0.924
Graded LASEC	0.754 ± 0.065*	0.000	0.627–0.881
CHA_2DS_2–Vasc	0.720 ± 0.065#	0.001	0.592–0.848
Qualitative LASEC	0.692 ± 0.060*	0.005	0.574–0.810
$CHADS_2$	0.668 ± 0.073#	0.014	0.525–0.811
Left Atrial Thrombus	0.648 ± 0.074*	0.030	0.502–0.794
*p < 0.01 vs. VI value, #p < 0.05 vs. VI value.			

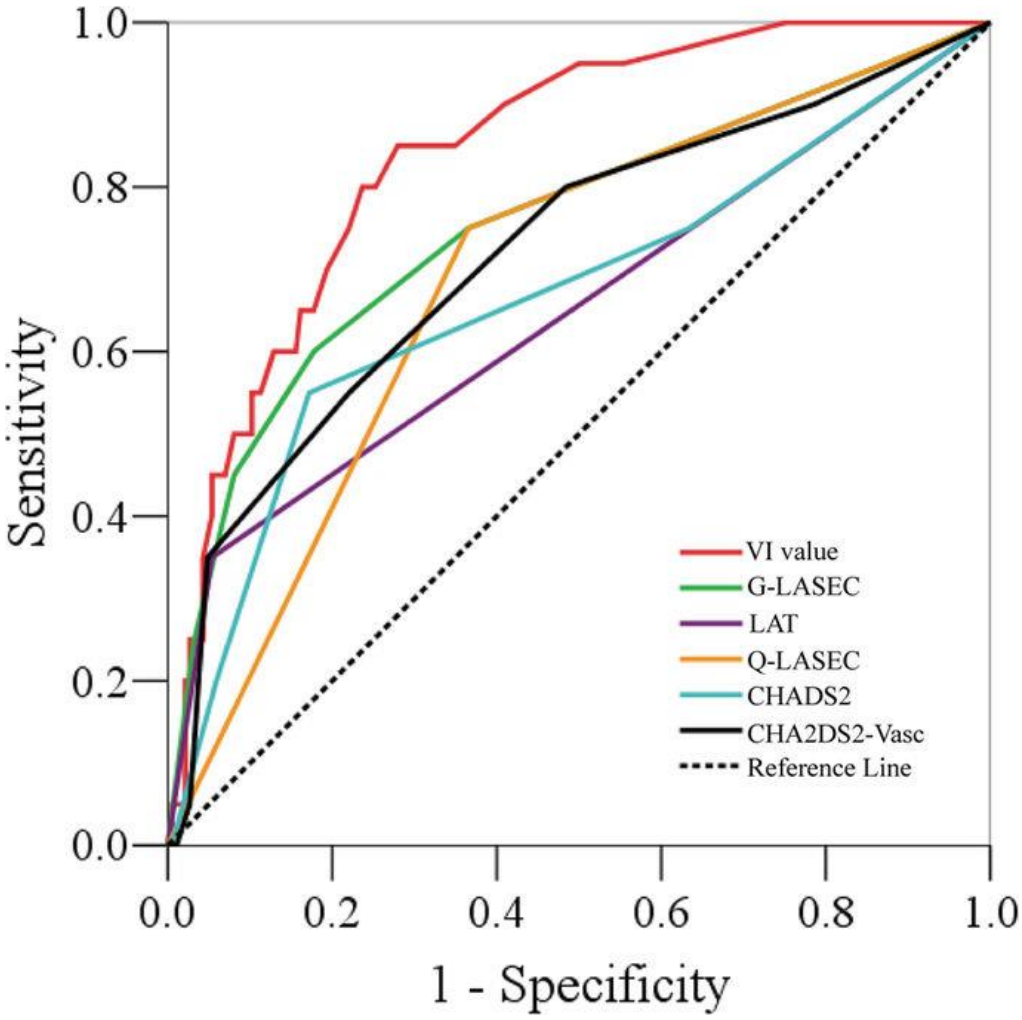


Figure 1.1.2 ROC curves analysis of VI value, Graded-LASEC (G-LASEC), CHA2DS2-Vasc, qualitative LASEC (Q-LASEC), LAT and CHADS2 in predicting the risk of stroke in patients with NVAF

The value of any diagnostic test is also reliant upon the reference standard or current gold standard for diagnosis against which it is judged. Any uncertainty in the reference standard will influence the performance of the diagnostic test under consideration. In stroke the gold standard diagnostic test has evolved over recent years and comprises a combination of expert clinical judgement and neuroimaging (Birenbaum *et al.*, 2011; Musuka *et al.*, 2015).

1.1.8 Stroke mimic conditions

Stroke is a complex condition which can present with a wide range of symptoms, the commonest of which are identified by the FAST. Other conditions also present with symptoms commonly associated with stroke and when mistaken for stroke are known as SM. Gibson and Whiteley's systematic review of SM included 29 studies describing SM identified in ambulances, ED, stroke units, primary care and other settings and concluded that 26% of all suspected stroke were SM, although this figure was based on highly heterogeneous studies (Gibson and Whiteley, 2013). They reported the 20 most common differential diagnoses of suspected stroke patients which shows the wide range of conditions mistaken for stroke, their table is replicated below:

Table 1.1.4 The 20 most common differential diagnoses of suspected stroke

Differential diagnosis	**Percentage of patients (n=813)**
Seizure	19.6
Syncope	12.2
Sepsis	9.6
Benign headache disorder	9.0
Brain tumour	8.2
Functional	7.4
Metabolic	6.2
Not specified	5.0
Neuropathy	4.6
Vertigo	3.2
Dementia	2.3
Extra- or subdural haemorrhage	1.8
Drugs and alcohol	1.6
Transient global amnesia	1.4

Table 1.1.4 The 20 most common differential diagnoses of suspected stroke cont.	
Differential diagnosis	**Percentage of patients (n=813)**
Myelopathy	1.0
Hypertension related	0.9
Parkinson's disease	0.7
Encephalopathy	0.5
Trauma	0.5
Invasive procedure	0.4

Gibson and Whiteley's work summarised the range of SM conditions using pre-determined diagnostic categories, but it included only 3 pre-hospital cohorts out of 29 so it has limited utility for this group of patients. Also, they did not describe characteristics that would help identify SM patients, although they did refer to the performance of the FAST and how FAST negative suspected stroke patients were less likely to have a stroke diagnosis (OR 0.4, 95% CI 0.3-0.6).

Long and Koyfman (Long and Koyfman, 2017) described the presentation and management of common SM for the emergency medicine physician which highlights that many stroke and SM patients will be seen by other healthcare professionals before they get to specialist stroke services.

Whilst focussing upon stroke care, it is also important to remember that SM patients have an underlying condition that needs to be assessed and treated appropriately. Good pre-hospital care is about getting the right patient, to the right place at the right time. The misdiagnosis of SM impacts on patients, ambulance services and stroke services. Patients may bypass local hospitals to access distant stroke services which places them away from local re-enablement services and supportive friends and family. Transporting a SM to a distant stroke centre means that ambulance crews are unavailable for an unnecessarily extended time. It may also necessitate a second ambulance to be called if the patient needs repatriation to their local hospital. There are also risks involved with transporting patients under emergency conditions (Lutman *et al.*, 2008; Sanddal *et al.*, 2010) which could potentially be avoided if the patient was diagnosed with a SM rather than a stroke.

The impact of SM in different models of care has been considered and becomes particularly relevant when stroke care centralisation is considered. Bypassing local hospitals to access specialist stroke services with SM patients, impacts on the patient, the ambulance service and the stroke services. Recent data on patients admitted to UK HASUs revealed that a sizable proportion (24-64%) of patients admitted to HASUs were SM (Alonge *et al.*, 2013; Shribman *et al.*, 2013; Siddiqui *et al.*, 2013; Aravind *et al.*, 2015; Dawson *et al.*, 2016; Sharobeem *et al.*, 2016).

Dawson et al (Dawson *et al.*, 2016) examined the bed use and length of stay of SM in a London HASU. They reported that SM accounted for 8-17% of HASU beds despite relatively short lengths of stay. They also recognised that advanced imaging like Magnetic Resonance Imaging (MRI) could be used to rapidly identify these patients as SM although this does have resource implications. They concluded that SM need to be accounted for when designing stroke pathways and systems. This work was referred to when the feasibility of implementing a regional HASU model of care across the UK was considered (Allen *et al.*, 2017). They reported that if stroke units were centralised into large regional HASUs the number of SM would need to be considered in terms of workforce and infrastructure impact.

Stroke services are a specialist and limited resource. Care on a HASU is more expensive than care on a general ward due to the specialist nature of the HASU. Bed days on a HASU are approximately three times more expensive than beds days on a general ward (£583 versus £181 based on 2010 costs (The Comptroller and Auditor General, 2010)). Therefore reducing the use of stroke services by SM should allow limited, specialist resources to be targeted at the intended recipients.

1.1.9 SM identification tools

SM identification has been explored by multiple authors and tools have been developed to identify SM. The tools described (summarised in table 1.1.5) were identified during the development of this project and supplemented by papers identified during the systematic review described in the next chapter. All of the studies were based on cohorts of hospitalised suspected stroke patients. The tools developed consistently included predictive variables from an epidemiological perspective such as age, seizures and the absence of vascular risk factors. Since the early work by Libman et al multivariate logistic regression has been the method used by all the studies apart from the Siddiqui et al paper. The focus of

some of the tools (Chang et al, Goyal et al and Hand et al) is described as informing and streamlining the acute assessment process and supporting the decision making around performing advanced imaging which makes sense in the context of the short time window for thrombolysis.

The performance characteristics of the tools were reported using multiple measures but Libman et al, Siddiqui et al and Tobin et al all reported high specificity with low sensitivity. Ali et al, Chang et al and Hand et al report good overall tool performance based on AUC. Goyal et al described very good performance in terms of sensitivity, specificity and PPV but this is in a population selected following negative CT imaging.

Tobin et al developed a tool on a small (n=206) sample of thrombolysis patients and only included three predictive variables. This paper was unusual in that it stated the tool developed was not clinically useful. They highlighted the neurological basis of many of the SM and recommended specialist stroke/neurology input for these patients. Merino et al also recommended specialist input despite describing predictive variables in a large dataset. Obviously, easy access to specialist input is impractical in pre-hospital assessment.

Although the work by Merino et al, Newey et al and Nor et al was not intended to specifically define a SM identification tool, it is included due to the similar intention and methods used and the similarities in the predictive factors reported. The work by Nor et al on the ROSIER tool showed that SM identification can be incorporated into a tool intended to improve stroke identification. None of the tools described were intended for the pre-hospital setting. The Chang et al and Siddiqui et al papers were based on populations of thrombolysed patients which does not translate easily to pre-hospital care. Ali et al, Chang et al, Hand et al and Newey et al included variables that are not commonly collected or available in pre-hospital care such as NIHSS and CT results, however the potential to develop a SM identification tool, based on readily available data, is clearly demonstrated by these studies.

The majority of the variables considered by the studies described above are collected and available in the pre-hospital setting, although the reliability during standard patient assessment is unclear. SM identification has not been previously considered in the pre-hospital setting but, based on the precedent set by these studies and with sufficient awareness of the information available to paramedics and their views on feasibility, it could be.

Table 1.1.5 Stroke mimic tools							
Author	**Year**	**Tool creation process**	**Setting**	**SM rate**	**Predictive variables included**	**Performance**	**Comments**
Stroke mimic tools							
Ali et al	2014	Univariate and multivariate logistic regression analysis of retrospective data. Derivation cohort 829 patients, internal validation cohort 332 patients, external validation cohort 226 patients	American telestroke network	23%	Age; AF; hypertension; seizure; facial weakness; NIHSS>14	Derivation AUC 0.75, internal AUC 0.71, external AUC 0.77	Based on data available at ED
Ali et al	2016	External validation of telestroke score descibed above in 1,985 consults	American and German telestroke systems	35%	As above	AUC 0.70	Validation of telestroke score described above
Chang et al	2012	Univariate and multivariate logistic regression analysis of retrospective data on 193 patients treated with tPA	American single centre	16%	Atherosclerosis on CTA; focal weakness; chest pain	Correct identification of 95.3% stroke patients and 60% SM patients. Overall accuracy 90.2%	Proposed model to help identify patients needing further tests prior to tPA
Goyal et al	2016	Univariate and multivariate logistic regression analysis of retrospective data. Derivation cohort 303 patients, validation cohort 481 patients	American multi-centre	41%	Facial weakness: AF; age; SBP; seizures; isolated sensory symptoms without weakness	FABS≥3 identifies SM with 90% sensitivity, 91% specificity, 87% PPV, 93% NPV	Designed for stroke response teams with negative CT patients to guide further imaging
Hand et al	2006	Univariate and multivariate logistic regression analysis of prospective data on 350 presentations with suspected stroke	UK single centre	31%	Known cognitive impariment; exact onset determined; focal neurological symptoms; abnormal vascular findings; NIHSS; lateralized signs; OSCP classification	Hosmer and Lemeshow P=0.746. 83% correct classifications. AUC 0.87	Intended to focus and streamline clinical assessment
Libman et al	1995	Univariate and multivariate logistic regression analysis of prospective data on 411 patients admitted to hospital with suspected stroke	American single centre	19%	Decreased level of consciousness; angina	Sensitivity 21%, specifcity 96%	Only patients admitted included in analysis. Unlcear when diagnosis made and if imaging used
Siddiqui et al	2016	Tool developed based on literature review using odds ratios to quantify strength of association. Tool tested using retrospective analysis of 106 patients treated with tPA	American single centre	25%	Age; hypertension; hyperlipidemia; diabetes; AF; migraine; epilepsy; psychiatric illness	Tool≥5 points identifes SM with 100% specifcity	Poster abstract so limited information
Tobin et al	2009	Multivariate logistic regression of retrospective data on 206 stroke alert patients amenable to tPA	American single centre	22%	Initial lateralizing signs; history of actue cerebrovascular event; DBP	Sensitivity 7%, specificity 99%	Some prehopsital data included. Conclusion that score is not clinically useful
Relevant to stroke mimic tool development							
Merino et al	2013	Univariate and multivariate logistic regression analysis of prospective data on 8,1987 patients with suspected stroke	American multi-centre	30%	Age; race; symptoma cuity; locatio; hypertension; hyperlipidemia; AF	N/A	Predictive factors described but not combined into a tool
Newey et al	2012	Univariate and multivaraite logistic regression analysis of prospective data on 93 inpatient stroke calls	American	39%	NIHSS item 1b; normal mental status; hand weakness; hemiparesis (all indicative of stroke)	N/A	Poster abstract so limited information. Predictive factors described but not combined into a tool
Nor et al	2005	Univariate and multivariate logistic regression of prospective data informed by clinical judgement. Development cohort 343 patients, temporal validation cohort 160 patients. All patients referred to stroke team	UK single centre	37%	Seizures; loss of consciousness (both indicative of SM)	N/A	Tool designed to identify stroke patients in the ED. TIA patients excluded. Does inlcude variables predictive of SM diagnosis

1.1.10 Clinical prediction rules

Stroke identification tools and SM identification tools are both examples of clinical prediction rules. "*Clinical prediction rules are mathematical tools that are intended to guide clinicians in their everyday decision making*." (Adams and Leveson, 2012).

Clinical prediction rules come under many different names: prognostic tools; decision support aids; prediction models and other variations. In summary these are tools that aid in decision making, usually by predicting a patient's outcome state. These tools are useful as they can inform decision making based on previous research with access to large datasets, help standardise decision making and allow the probabilities of various outcomes to be quantified. The clinical prediction rule developed in this work shall be referred to as a tool.

There are numerous methods for developing clinical prediction tools (Adams and Leveson, 2012) but the basic process involves four steps:

1. Development of a tool that identifies the condition of interest.
2. Validation that the tool performs as expected in a new population.
3. Impact analysis of what difference the tool would make in practice.
4. Implementation of the tool into regular healthcare.

Steps one to three were described in greater depth in a series of prognostic research papers (Altman *et al.*, 2009; Moons *et al.*, 2009a; Moons *et al.*, 2009b; Royston *et al.*, 2009) which were summarised by Steyerberg et al (Steyerberg *et al.*, 2013). These three steps guided the methods chosen for this project, fit within the development section of the MRC complex interventions framework (Craig *et al.*, 2008) and are expanded upon in later chapters. Step four in the above process will not be completed within the scope of this project, but factors that would aid or hinder future implementation will be explored with professional stakeholders in chapters 2.1, 2.3 and 3.3.

1.1.11 Summary

This chapter has described advances in stroke care which require stroke patients to be accurately identified and directed to stroke services, often within limited time windows, but with the drawback that SM conditions are also caught up in the emergency assessment pathway. Misdiagnosis of SM causes problems for patients, ambulance services and stroke services but identification of SM has been shown to be possible in hospital cohorts using

simple clinical characteristics. Based on this there is an opportunity to improve pre-hospital stroke care through the development of a pre-hospital SM identification tool.

The next chapter contains a systematic review of the literature describing SM including the frequency with which SM are documented, the conditions causing SM and clinical characteristics that may be associated with SM. This systematic review was used to inform the development of the initial SM tool and the remainder of this thesis.

Chapter 1.2 The frequency, characteristics and aetiology of stroke mimic presentations: a narrative review

1.2.1 Introduction

This chapter reports the findings of a systematic review of the literature investigating the frequency, characteristics and aetiology of SM. Due to the scarcity of pre-hospital specific literature this review describes SM across a broad range of settings.

As described in the previous chapter, a number of studies have developed tools to identify SM (Merino *et al.*, 2013; Ali *et al.*, 2014; Goyal *et al.*, 2016b) using characteristics associated with SM diagnosis, such as patient age or presence of seizures, along with the absence of factors associated with stroke diagnosis, such as Atrial Fibrillation (AF) or hypertension. However these tools are not in widespread use and have not been studied in pre-hospital settings where they may perform differently due to the different population, the limited information available to paramedics and their clinical interpretation. This review will report on literature describing the frequency and characteristics of SM in order to inform the development of a similar SM identification tool but with a pre-hospital focus.

This chapter was published in the European Journal of Emergency Medicine in May 2018 as a stand-alone review (McClelland *et al.*, 2018).

1.2.2 Methods

A systematic search was performed with the results reported using narrative synthesis. The review protocol was prospectively registered on PROSPERO (registration number 42015026457) (McClelland *et al.*, 2015). This review is reported following the PRISMA statement (Moher *et al.*, 2009).

1.2.2.1 Inclusion criteria

To be eligible for inclusion studies had to fulfil the following criteria:

- Primary studies describing adult (18 years and above) patients with initial diagnosis of stroke and final non-stroke diagnosis.
- Reported a number and/or rate of SM.
- Reported the clinical and/or demographic characteristics of a SM population.

- Published in the English language.

Case reports were excluded from the review.

1.2.2.2 Database search strategy

A simple but structured search strategy (appendix A) was developed with input from an information specialist. This was applied to the following databases up to February 2017: MEDLINE; EMBASE; PsycInfo; CINAHL; Cochrane Database of Systematic Reviews and Database Of Research In Stroke. Grey literature was identified using the first 30 pages of Google and Google Scholar (Haddaway *et al.*, 2015).

1.2.2.3 Study selection process

Studies were screened based upon title and abstract by one reviewer (GM) with uncertainties discussed with another member of the review team. Abstracts which appeared relevant were assessed for eligibility in full text format by the same reviewer (GM). The reference lists of all studies included were hand searched. Citation searching of included studies was undertaken using ISI Web of Science.

1.2.2.4 Data extraction and analysis

Data were extracted using a structured form to capture the following: title; authors(s); journal; year; country; setting; proportion of SM; stroke assessment tool; method of stroke diagnosis; method of SM diagnosis; presence of SM final diagnosis; demographics and/or clinical characteristics.

Clinical Classification Software (CCS) codes were used to combine SM diagnoses reported within studies using variable terminology into clinically relevant groups (Healthcare Cost and Utilization Project, 2017).

Due to the descriptive aims of the review, variability in the definition of stroke and SM and the anticipated heterogeneity of studies with variable quality there was no pre-specified meta-analysis.

1.2.2.5 Quality assessment

Due to anticipated heterogeneity within the literature the Quality Assessment Tool for Studies with Diverse Designs (QATSDD) was preselected for assessing study quality (Sirriyeh *et al.*, 2012). This tool was not applied to abstracts.

1.2.3 Results

The search strategy yielded 9,972 references. After initial screening 336 full text articles were reviewed. The screening process is summarised in figure 1.2.1.

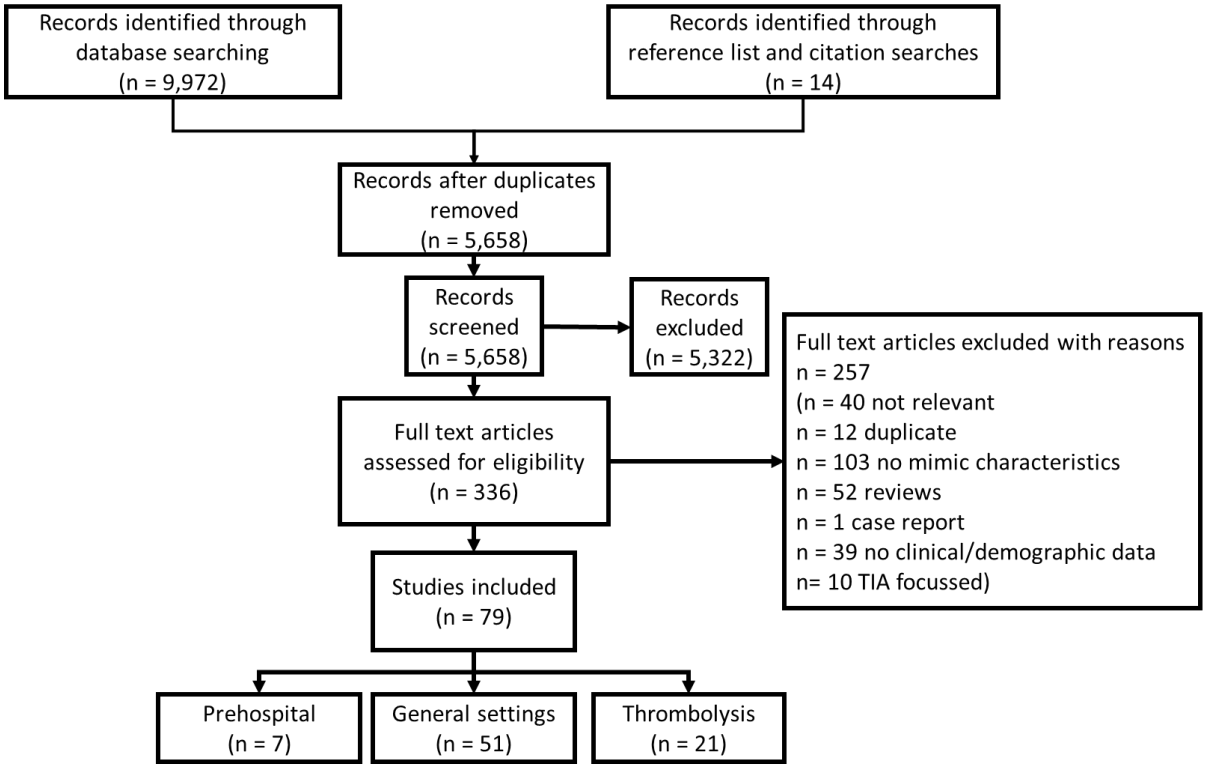


Figure 1.2.1 Flowchart summarising study selection process

Seventy-nine studies (table 1.2.1) were included in the review. The median year of publication was 2013 (range 1982-2017). The majority of studies originated from North America (n=34, 43%) or Europe (n=29, 37%). The majority (n=78, 99%) of studies were cohort studies with 41 (53%) collecting data prospectively, 36 (46%) retrospectively and in 1 (1%) study the direction of data collection was unclear.

The overall population included 147,779 patients. SM patients were younger than stroke patients (pooled mean age 61.7 vs 69.6 years) with a higher percentage of females (pooled female gender 53.3% vs 47.7%). Included studies were described as three groups. Those with populations confined to pre-hospital settings (n=7) reflect the early identification of suspected stroke patients, usually through application of specific tools and protocols. Thrombolysis studies (n=21) are separately described as these have a clearly defined sub-population based upon the criteria for administration of a specific treatment. All other studies (n=51) were not uniquely pre-hospital or thrombolysis focussed.

Table 1.2.1 Studies included in the systematic review								
Authors	**Year**	**Country**	**Design**	**Setting**	**Sample size**	**SM (%)**	**Stroke identification tool used**	**QATSDD score (%)**
General settings								
Aiyesimoju et al (Aiyesimoju *et al.*, 1983)	1983	Nigeria	Retrospective cohort	Hospital	152	9	NR	43
Ali et al (Ali *et al.*, 2014)	2014	USA	Retrospective cohort	Tele	1387	23	NR	U
Ali et al (Ali *et al.*, 2016)	2016	USA, Germany	Cohort	Tele	1985	35	NR	55
Alonso et al (Alonso *et al.*, 2014)	2014	Spain	Prospective cohort	ED	140	26	NR	U
Alves et al (Alves *et al.*, 2016)	2016	Portugal	Retrospective cohort	Stroke unit	367	12	NR	36
An et al (An *et al.*, 2013)	2013	Korea	Prospective cohort	Hospital	278	32	NR	64
Ay et al (Ay *et al.*, 1999)	1999	USA	Retrospective cohort	Hospital	27	37	NR	48
Barker et al (Barker *et al.*, 1984)	1984	USA	Prospective cohort	Hospital	1604	44	NR	55
Brunser et al (Brunser *et al.*, 2013)	2013	Chile	Prospective cohort	ED	842	13	NR	57
Clarey et al (Clarey *et al.*, 2014)	2014	Australia	Prospective cohort	GP	179	51	NR	76
Dassan et al (Dassan *et al.*, 2012)	2012	UK	Prospective cohort	Stroke unit	44	34	NR	52
Dawson et al (Dawson *et al.*, 2016)	2016	UK	Retrospective cohort	HASU	2305	24	NR	62

Table 1.2.1 Studies included in the systematic review cont.

Authors	Year	Country	Design	Setting	Sample size	SM (%)	Stroke identification tool used	QATSDD score (%)
Delva et al (Delva *et al.*, 2015)	2015	Ukraine	Retrospective cohort	Hospital	2219	8	NR	U
Eichel et al (Eichel *et al.*, 2013)	2013	Israel	Retrospective cohort	Hospital	124	63	NR	67
El Husseini and Goldstein (El Husseini and Goldstein, 2013)	2013	USA	Retrospective cohort	Hospital	297	56	NR	45
Ferro et al (Ferro *et al.*, 1998)	1998	Portugal	Prospective cohort	Hospital	237	9	NR	50
Foerch et al (Foerch *et al.*, 2012)	2012	Germany /Switzerland	Prospective cohort	Hospital	205	3	NR	57
Gargalas et al (Gargalas *et al.*, 2017)	2017	UK	Retrospective cohort	HASU	1165	22	NR	76
Gonzalez-Garcia et al (Gonzalez-Garcia *et al.*, 2012)	2012	Cuba	Prospective cohort	Stroke unit	72	15	NR	43
Goyal et al (Goyal *et al.*, 2016b)	2016	USA, Greece	Prospective cohort	ED	784	41	NR	67
Hammermeister et al (Hammermeister *et al.*, 2013)	2013	USA	Retrospective cohort	ED	1002	47	NR	U
Hand et al (Hand *et al.*, 2006)	2006	Australia/UK	Prospective cohort	Hospital	350	31	NR	79

Table 1.2.1 Studies included in the systematic review cont.

Authors	Year	Country	Design	Setting	Sample size	SM (%)	Stroke identification tool used	QATSDD score (%)
Hatzitolios et al (Hatzitolios *et al.*, 2008)	2008	Greece	Retrospective cohort	Stroke unit	362	5	NR	38
Hemmen et al (Hemmen *et al.*, 2008)	2008	USA	Retrospective cohort	ED	411	25	NR	60
Jiang et al (Jiang *et al.*, 2014)	2014	China	Prospective cohort	ED	715	48	NR	79
Knauer et al (Knauer *et al.*, 2012)	2012	Germany	Prospective cohort	Stroke unit	174	28	NR	69
Kose et al (Kose *et al.*, 2013)	2013	Turkey	Retrospective cohort	ED	671	13	NR	52
Kothari et al (Kothari *et al.*, 1995)	1995	USA	Retrospective cohort	ED	441	4	NR	62
Laskowitz et al (Laskowitz *et al.*, 2009)	2009	USA	Prospective cohort	Hospital	1289	40	NR	79
Libman et al (Libman *et al.*, 1995)	1995	USA	Prospective cohort	ED	411	19	NR	40
Luger et al (Luger *et al.*, 2017)	2017	Germany	Prospective cohort	Hospital	202	5	NR	71
Mao et al (Mao *et al.*, 2016)	2016	China	Prospective cohort	ED	416	14	NR	48
Martin et al (Martin *et al.*, 1997)	1997	UK	Prospective cohort	Hospital	508	27	NR	64
Merino et al (Merino *et al.*, 2013)	2013	USA	Prospective cohort	Hospital	8187	30	NR	67

Table 1.2.1 Studies included in the systematic review cont.

Authors	Year	Country	Design	Setting	Sample size	SM (%)	Stroke identification tool used	QATSDD score (%)
Montaner et al (Montaner *et al.*, 2011)	2011	Spain	Prospective cohort	ED	1005	9	NR	76
Natteru et al (Natteru *et al.*, 2016)	2016	USA	Retrospective cohort	Hospital	93	39	NR	55
Nor et al (Nor *et al.*, 2005)	2005	UK	Prospective cohort	ED	516	44	NR	69
Norris and Hachinski (Norris and Hachinski, 1982)	1982	Canada	Retrospective cohort	Stroke unit	821	13	NR	33
O'Brien et al (O'Brien *et al.*, 1987)	1987	Ireland	Prospective cohort	Hospital	100	1	NR	57
O'Connell et al (O'Connell *et al.*, 2016)	2016	USA	Prospective cohort	Hospital	89	NR	NR	64
Pearson et al (Pearson *et al.*, 2017)	2017	USA	Prospective cohort	ED	114	43	NR	U
Penn et al (Penn *et al.*, 2016)	2016	Canada	Prospective cohort	ED	40	NR	NR	U
Quenardelle et al (Quenardelle *et al.*, 2016)	2016	France	Prospective cohort	Hospital	1361	38	NR	69
Ramadan et al (Ramadan *et al.*, 2015)	2015	UK	Prospective cohort	Hospital	916	28	NR	U
Reid et al (Reid *et al.*, 2012)	2012	UK	Retrospective cohort	Stroke unit	375	31	NR	48
Sharma et al (Sharma *et al.*, 2014)	2014	USA	Prospective cohort	Hospital	167	22	NR	76

Table 1.2.1 Studies included in the systematic review cont.

Authors	Year	Country	Design	Setting	Sample size	SM (%)	Stroke identification tool used	QATSDD score (%)
Taguchi et al (Taguchi *et al.*, 2016)	2016	Japan	Prospective cohort	Hospital	353	28	NR	45
Tobin et al (Tobin *et al.*, 2009)	2009	USA	Retrospective cohort	ED	206	22	NR	60
Tuntiyatorn et al (Tuntiyatorn *et al.*, 2013)	2013	Thailand	Retrospective cohort	ED	704	26	NR	62
Whiteley et al (Whiteley *et al.*, 2011)	2011	UK	Prospective cohort	ED	356	31	NR	74
Wolf et al (Wolf *et al.*, 2016)	2016	Germany	Prospective cohort	ED	410	64	NR	45
Prehospital								
Brandler et al (Brandler *et al.*, 2015)	2015	USA	Retrospective cohort	PH	736	36	CPSS	74
Bray et al (Bray *et al.*, 2005)	2005	Australia	Prospective cohort	PH	100	27	MASS	69
Gioia et al (Gioia *et al.*, 2016)	2016	Canada	Retrospective cohort	PH	960	43	CPSS	60
Karlinski et al (Karlinski *et al.*, 2015)	2015	Poland	Prospective cohort	PH	570	37	Physician judgement	57
Restrepo et al (Restrepo *et al.*, 2010)r	2010	USA	RCT	PH	567	4	LAPSS	U
Sequeira et al (Sequeira *et al.*, 2016)	2016	USA	Retrospective cohort	PH	3376	19	CPSS	57

Table 1.2.1 Studies included in the systematic review cont.

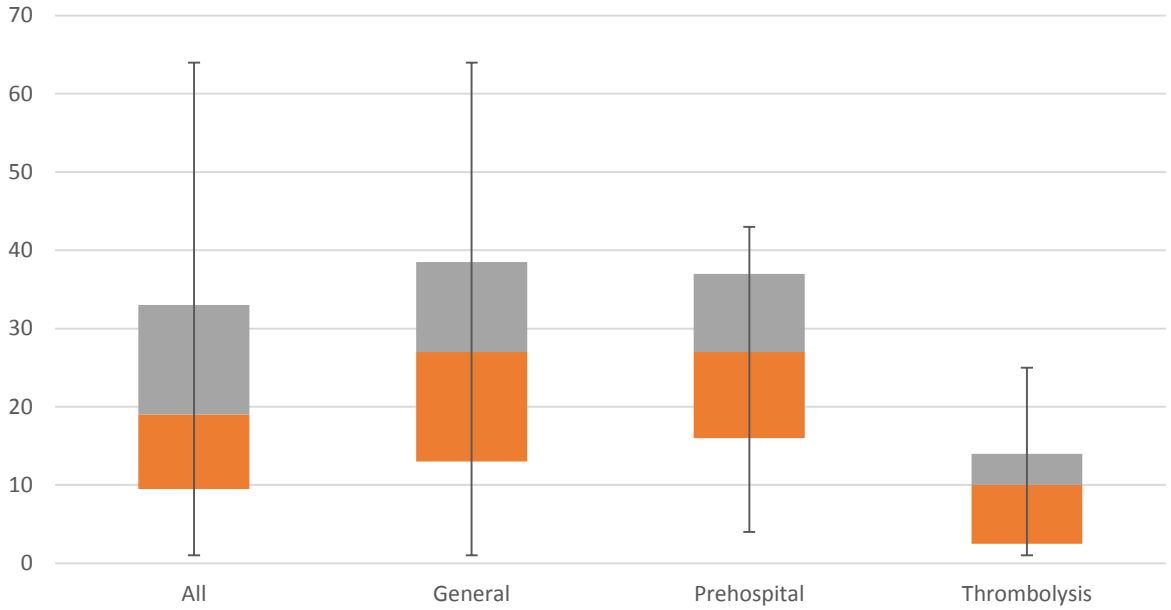
Authors	Year	Country	Design	Setting	Sample size	SM (%)	Stroke identification tool used	QATSDD score (%)
Wendt et al (Wendt *et al.*, 2015)	2015	Germany	Prospective cohort	PH	561	16	Unclear	69
Thrombolysis								
Artto et al (Artto *et al.*, 2012)	2012	Finland	Retrospective cohort	Stroke unit	985	1	NR	69
Asaithambi et al (Asaithambi *et al.*, 2017)	2017	USA	Retrospective cohort	Tele	131	10	NR	45
Chang et al (Chang *et al.*, 2012)	2012	USA	Retrospective cohort	Hospital	193	16	NR	50
Chen et al (Chen *et al.*, 2011)	2011	France/Serbia	Retrospective cohort	Stroke unit	488	1	NR	50
Chernyshev et al (Chernyshev *et al.*, 2010)	2010	USA	Retrospective cohort	ED	512	14	NR	52
Forster et al (Forster *et al.*, 2012)	2012	Germany	Prospective cohort	Hospital	648	7	NR	69
Goyal et al (Goyal *et al.*, 2015)	2015	USA	Retrospective cohort	Hospital	535	14	NR	69
Guillan et al (Guillan *et al.*, 2012)	2012	Spain	Prospective cohort	Hospital	621	2	NR	55
Lewandowski et al (Lewandowski *et al.*, 2015)	2015	USA	Retrospective cohort	ED	323	12	NR	52
Liberman et al (Liberman *et al.*, 2015)	2015	USA	Prospective cohort	Hospital	121	14	NR	55

Table 1.2.1 Studies included in the systematic review cont.

Authors	Year	Country	Design	Setting	Sample size	SM (%)	Stroke identification tool used	QATSDD score (%)
Mehta et al (Mehta *et al.*, 2014)	2014	USA	Retrospective cohort	Stroke unit	120	17	NR	52
Rostanski et al (Rostanski *et al.*, 2016)	2016	USA	Retrospective cohort	ED	350	14	NR	55
Sarikaya et al (Sarikaya *et al.*, 2012)	2012	Switzerland	Prospective cohort	Hospital	326	7	NR	60
Scott and Silbergleit (Scott and Silbergleit, 2003)	2003	USA	Retrospective cohort	Hospital	151	4	NR	62
Siddiqui et al (Siddiqui *et al.*, 2016)	2016	USA	Retrospective cohort	Hospital	106	25	NR	U
Sivakumaran et al (Sivakumaran *et al.*, 2016)	2016	UK	Retrospective cohort	HASU	489	10	NR	50
Tsivgoulis et al (Tsivgoulis *et al.*, 2015)	2015	USA	Prospective cohort	Hospital	516	15	NR	83
Tsivgoulis et al (Tsivgoulis *et al.*, 2011)	2011	USA	Retrospective cohort	Hospital	539	10	NR	64
Winkler et al (Winkler *et al.*, 2009)	2009	Switzerland	Prospective cohort	Stroke unit	250	3	NR	60
Xian et al (Xian *et al.*, 2016)	2016	USA	Retrospective cohort	Hospital	90746	1	NR	U
Zinkstok et al (Zinkstok *et al.*, 2013)	2013	Europe	Prospective cohort	Hospital	5581	2	NR	62

The pooled mean and median SM rates were 22% (SD 16%) and 19% (IQR 9.5-33%) respectively. The median SM rates were 27% (IQR 13-38.5%) in the general group, 27% (IQR 16-37%) in the pre-hospital group and 10% (IQR 2.5-14%) in the thrombolysis group. These SM rates are summarised in chart 1.2.1.

Chart 1.2.1 Box plot showing median, IQR and range of stroke mimic rates



QATSDD scoring was converted into an overall percentage for each study to simplify comparison. Included studies scored a median 60% (IQR 52-69) on the QATSDD (see appendix B). The three subgroups had similar pooled mean scores on the QATSDD: pre-hospital 64%; mixed 59% and thrombolysis 59%. As a sensitivity analysis the studies scoring below the lower QATSDD quartile were compared with studies scoring above the upper quartile. The lowest quartile studies (n=17) reported a pooled mean SM rate of 21% (SD 17.5) based on 5,601 patients and the highest quartile studies (n=11) reported a pooled mean SM rate of 28% (SD 15.1) based on 6,680 patients.

1.2.3.1 SM final diagnoses

Sixty-three studies (80%) reported the SM underlying diagnoses. Methods of identifying the diagnosis of SM included: discharge/final diagnosis (40%); neurologist or stroke specialist assessment (17%); expert panel (14%); registry (6%); and other/unclear (22%). There was insufficient information presented to make objective assumptions that any one approach

was superior or inferior, and the investigator choice of reference standard did not exclude studies.

SM diagnoses were summarised using CCS codes (Healthcare Cost and Utilization Project, 2017). This resulted in 103 initial CCS codes, which were reported using level 1 CCS (broad disease categories) and level 2 CCS (more specific disease areas) codes (figure 1.2.3).

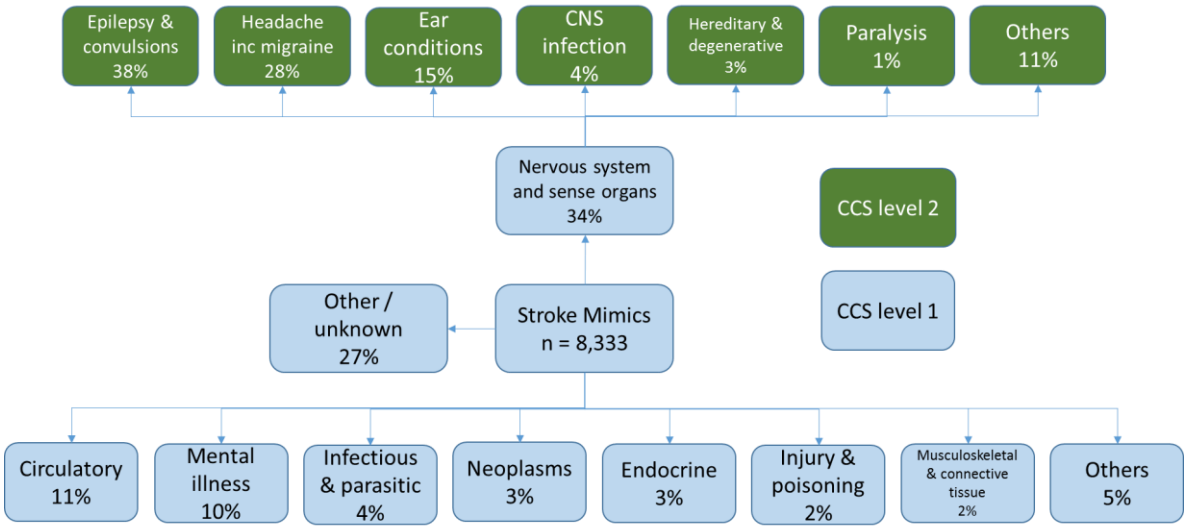


Figure 1.2.3 Taxonomy of SM using CCS codes

1.2.3.2 Pre-hospital studies

Seven (9%) studies clearly described pre-hospital settings: 6,870 patients, mean SM rate 26% (SD 14%). SM patients were younger than stroke patients (67 vs 73 years pooled mean age) with a higher proportion of females (SM 58% female vs stroke 49% female).

The most frequent level 1 CCS diagnostic groups in the pre-hospital setting were: diseases of the nervous system and sense organs (29%); symptoms, signs and ill-defined conditions and factors influencing health status (9%) and unknown (43%). The most frequent level 2 CCS diagnostic groups were: epilepsy and convulsions (19%); symptoms, signs and ill-defined conditions (9%) and ear conditions (5%).

1.2.3.3 Thrombolysis studies

Twenty-one (26%) studies described SM in patients treated with thrombolysis: 103,731 patients, mean SM rate 9% (SD 7%). SM patients were younger than stroke patients (57 vs 68 years mean age). More SM patients were female (SM pooled mean 57% vs stroke 46%).

The most frequent level 1 CCS diagnostic groups in the thrombolysis cohorts were: diseases of the nervous system and sense organs (37%); mental illness (18%) and unknown (42%). The most frequent level 2 CCS diagnostic groups were: miscellaneous mental disorders (17%); headache including migraine (17%); and epilepsy and convulsions (16%).

1.2.3.4 General studies

Fifty-one (65%) studies described cohorts that were not specifically identified as pre-hospital or receiving thrombolysis: 37,178 patients, mean SM rate 27% (SD 16%). These settings included: hospital (41%); ED (35%); stroke unit/HASU (18%); telemedicine (4%); and general practice (2%). The total population was 50% male with a pooled mean age of 68 years. SM patients were younger than stroke (63 vs 70 years pooled mean age) with a higher proportion of females (SM 51% female vs stroke 48% female).

The most frequent level 1 CCS diagnostic groups were: diseases of the nervous system and sense organs (34%); diseases of the circulatory system (15%); mental illness (10%) and unknown (17%). The most frequent level 2 CCS diagnostic groups were: epilepsy and convulsions (10%); cerebrovascular disease e.g. TIA; subdural haemorrhage (9%); and headache including migraine (9%).

1.2.3.5 Clinical characteristics

Studies reporting clinical characteristics associated with SM are described in table 1.2.2. Associations between clinical characteristics and diagnosis were reported as positive for SM or stroke ($p<0.05$ or stated within text as significant) or non-significant.

Table 1.2.2 Characteristics associated with SM diagnosis reported by number of papers

	Characteristics	Associated with SM	No association	Associated with stroke
Past medical history	Diabetes	2	23	9
	Hypercholesterolemia	3	6	2
	Migraine	5	1	0
	Seizure	9	2	0
	Smoker	1	21	4
	Stroke	7	11	5
	TIA	1	2	1

Table 1.2.2 Characteristics associated with SM diagnosis reported by number of papers cont.

	Characteristics	Associated with SM	No association	Associated with stroke
Symptoms (negative)	Abnormal admission neurological examination	1	0	0
	Altered level of consciousness / mental status	9	5	1
	Aphasia	1	0	1
	Cognitive impairment	3	1	0
	Confusion	3	1	0
	Dysphagia	1	0	0
	General weakness	1	0	0
	Sensory deficit	4	0	0
Symptoms (positive)	Diabetic symptoms	1	0	0
	Dizziness / vertigo	5	3	0
	Headache	1	5	1
	Pain	1	0	0
	Psychiatric / somatic disorder	6	1	0
	Seizure	6	0	0
Other	Can walk now	1	0	0
	Neuro symptoms inconsistent with vascular territory	1	0	0
	No lateralising symptoms	1	0	0
	No motor or speech deficit	1	0	0
	No neurological signs	1	0	0
	Normal extraocular movements	1	0	0
	Normal Glasgow Coma Scale (GCS)	1	0	0

1.2.4 Discussion

This review identified SM studies with heterogeneous aims, settings, reference standards and reporting methods. The studies included had a wide range of QATSDD scores, however the subgroup mean scores were similar. As there were no pre-specified exclusion criteria based on quality assessment, all identified studies were included. The QATSDD identified that very few studies discussed sample size or considered the accuracy of the final diagnoses therefore an element of selection bias must be acknowledged.

These findings build on earlier work (Gibson and Whiteley, 2013) by showing that despite advancing technology and better availability of specialist assessment, SM continue to be a diagnostic challenge. To inform the development of screening processes with improved specificity, this review has described typical characteristics that may aid with SM diagnosis.

1.2.4.1 Frequency

The reported rate of SM was influenced by the clinical definition of stroke used at the time of the study and therefore varied across the literature (Staubach *et al.*, 2016). SM accounted for 22% of all suspected stroke cases, which is lower than the 26% previously reported (Gibson and Whiteley, 2013). This discrepancy may be the result of recent large thrombolysis cohorts being included (Zinkstok *et al.*, 2013; Xian *et al.*, 2016). Thrombolysis studies have a lower SM frequency because of the specialist assessment, treatment criteria and neuroimaging required to make treatment decisions. However, the pooled SM rates for the pre-hospital and general populations were similar at 27%. Studies in the upper quartile based on QATSDD scoring reported a higher SM rate (28%) than studies in the lower quartile (21%) so the combined figure may be an under-estimate.

The high frequency of SM in pre-hospital care may be due to a number of factors: most pre-hospital services are paramedic led; application of high sensitivity stroke identification instruments; insufficient time to assess in more detail to identify SM; availability of information about past medical history; and the lack of imaging or point of care diagnostics for stroke. Nevertheless, SM rates were similar in the pre-hospital and general groups. This may reflect that a significant portion of the general group were also unfiltered pre-hospital patients, and that apart from very obvious SM identified during initial ED assessment the initial diagnoses made in the pre-hospital setting were not over-ruled until later stroke specialist assessment with brain imaging.

The presence of SM in thrombolysis populations reflects the challenging nature of acute stroke treatment. The drive to reduce door-to-needle (DTN) time may be linked with increased SM thrombolysis (Liberman *et al.*, 2015). Thrombolysing SM has relatively low risks (Zinkstok *et al.*, 2013; Liberman *et al.*, 2015) but should not become an acceptable consequence of optimising stroke treatment, and it does have financial implications (Goyal *et al.*, 2015). Using current diagnostic processes this is a challenging area to address because of the lack of clear clinical characteristics differentiating stroke from SM, and the need to treat patients early to get the most benefit. Developments and investment in rapid advanced imaging to reveal positive evidence of acute ischaemia or the development of rapid biomarker tests would help avoid thrombolysis for some patients in this group (Bivard *et al.*, 2015).

1.2.4.2 Characteristics

SM patients tended to be younger than stroke patients and were more likely to be female. The mean age falls as patients move from pre-hospital care, to non-specialist care (general group) and on to specialist care (thrombolysis group). This may reflect the increasing rigour of the assessment process.

Clinical characteristics (table 1.2.2) were reported under a variety of overlapping terms. Due to methodological concerns a weighted average or meta-analysis was not conducted. The distribution of clinical characteristics across studies was used as a crude measure of association. Seizures, history of migraine and psychiatric disorders were the characteristics with the clearest association with SM diagnosis. There was disagreement between studies as to the direction of association for some characteristics e.g. history of stroke is associated with stroke (5 studies), SM (7 studies) and non-significant (12 studies). This reflects that although vascular risk factors are more likely to be present amongst stroke patients, their presence was also a reason for clinicians to wrongly suspect stroke as a cause for new symptoms. However as a stronger risk factor AF had a clearer relationship with stroke (26 studies positive association; 7 non-significant association).

Focal neurological deficits used by most identification scores maintained their relationship with stroke e.g. facial palsy/weakness (1 non-significant, 13 associated with stroke) (Loomis and Mullen, 2014; Lip and Lane, 2015). The absence of these characteristics could be an indicator of SM, and has been used in SM identification tools (chapter 1, table 1.1.5).

1.2.4.3 Aetiology

Many conditions present as SM and diagnostic methods, including the use of brain imaging, were highly variable in the literature. The definition of stroke, and therefore SM, varied and conditions such as TIA and sub-arachnoid haemorrhage were variably classified as stroke or SM. It is important that investigators transparently present data so that services can decide upon the relevance of the results.

The use of CCS codes allowed the findings of this heterogeneous dataset to be summarised. Disorders of the nervous system and sense organs were the most common cause of SM, particularly seizures which mirrors previous findings (Gibson and Whiteley, 2013). Some pre-hospital stroke tools used seizures to indicate a reduced likelihood of stroke (Kidwell *et al.*, 2000; Nor *et al.*, 2005) and some SM identification tools also included seizures (Ali *et al.*, 2014; Goyal *et al.*, 2016b). Accurate history taking is crucial, but seizures can be unwitnessed and it is only the gradual recovery, lack of acute changes on imaging, clarification of past medical history and further investigations which confirm the diagnosis. As 2% of acute stroke patients experience a seizure (Huang *et al.*, 2014), this is an area where development of rapid diagnostics may be helpful.

1.2.4.4 Clinical implications

Pre-hospital identification of SM may help to ensure that patients access appropriate pathways of care, especially in centralised service configurations which require a pre-hospital redirection decision. Application of a SM identification tool, such as those described in chapter 1.1, would support creation and evaluation of a two stage process. The initial stage is suspicion of stroke based on triggering a high sensitivity tool during clinical assessment such as FAST, the second stage is refinement of this initial diagnosis based upon a SM assessment with high specificity. This two stage assessment does not include the initial suspicion of stroke by the ambulance dispatch centre where high sensitivity to potential stroke is paramount. A recent study using CPSS guided dispatch of ambulances was able to identify 2/3rds of patients suitable for thrombolysis simply through structured telephone description of symptoms (Dami *et al.*, 2017), but there is currently no formalised pre-hospital equivalent score at dispatch to then identify patients who could be a SM.

Due to the lack of clinical characteristics that clearly differentiate strokes and SM, this second stage provides an opportunity to apply novel point of care diagnostic technologies

(Gonzalez *et al.*, 2013; Luger *et al.*, 2017) to improve the overall assessment performance. A SM assessment could also be used to help target specialist resources such as mobile stroke units (Fassbender *et al.*, 2017). These may also assist in early decision making about whether patients being assessed for thrombolysis should have additional imaging, other than CT, in order to minimize inappropriate treatment.

In the meantime, clinician knowledge of common SM characteristics could inform the differential diagnoses considered when assessing suspected stroke patients. Training programmes should encourage clinicians to seek additional information which might broaden the diagnosis for key demographic groups, rather than just stop their clinical assessment once stroke is suspected.

1.2.4.5 Limitations

Meta-analysis was not attempted due to the narrative nature of this review and study heterogeneity. A quality assessment tool tailored for cohort studies may have been more appropriate than the QATSDD tool which was chosen prior to study identification. The initial screening and identification was performed by a single reviewer so relevant studies could have been missed. Non-English studies were not included. CCS coding simplified cases to a single diagnostic category to aid reporting, but this does not represent the multiple problems some patients possess. The pre-hospital population was small reflecting the lack of clearly described pre-hospital research. The representation of clinical characteristics is crude but could be used to inform the focus of future studies.

1.2.5 Conclusions

Twenty-two percent of all suspected stroke patients had a SM condition. SM patients included a higher proportion of females and tended to be younger than stroke patients, but these are unsuitable criteria to use in isolation to make a clinical judgement. Many conditions present as SM but seizures and migraines are the most frequent aetiologies. It is challenging to identify clinically useful characteristics that differentiate SM from stroke, however a combination of stroke and SM assessment tools during the acute phase of emergency stroke care might reduce the number of false positive identifications created by commonly used symptom checklists.

1.2.6 Summary

This chapter has shown that pre-hospital care providers encounter and transport a large number of SM which will contribute to the high numbers seen in other settings. Although there was very little literature specific to pre-hospital care there were some consistent findings in terms of SM aetiology and characteristics of SM which will be used to inform the development of a pre-hospital SM tool. The next chapter reports a survey of paramedics' views about stroke care and their views on pre-hospital SM identification.

Chapter 1.3 Survey of UK Paramedics stroke training, practice and stroke mimic knowledge

1.3.1 Introduction

This chapter reports the results of a survey of UK paramedics seeking their views on stroke training, practice, knowledge about SM conditions and their views about pre-hospital identification of SM. A previous survey reported on EMS providers basic pre-hospital stroke knowledge and treatment in America (Crocco *et al.*, 2009) but this is not directly relevant to current UK practice due to healthcare system and temporal differences. This survey was conducted in order to inform the development of the SM tool.

This survey was necessary because the development, and deployment, of any initiative is more likely to succeed if the context in which it will be applied is understood (Craig *et al.*, 2008). This understanding was sought through stakeholder engagement throughout the development process. The views of paramedics about priorities for practice and their general background understanding of the topic would influence whether a SM identification tool could make a difference during patient care. If they were unwilling to act upon a SM tool output, or only under certain circumstances (e.g. if it indicated that there was a high probability of a SM diagnosis) then these views would influence the development, the training and the implementation within the standard care pathway.

This survey was supported by a small research grant from the College of Paramedics (CoP). The results of this survey were published in the British Paramedic Journal (McClelland *et al.*, 2017).

1.3.2 Chapter aims and objectives

The aim of this chapter is to describe paramedics' views about pre-hospital stroke care.

The objectives of this chapter are:

- Report paramedics' views about their stroke training.
- Describe current practice in UK pre-hospital stroke care.
- Assess how acceptable the idea of SM identification is to UK paramedics.

1.3.3 Methods

An online survey was used to generate descriptive data from an opportunistic sample of UK paramedics. The content reflected contemporary literature regarding identification and treatment of patients with suspected stroke in the pre-hospital setting. To ensure clarity and relevance, the survey was piloted within the North East region of England with paramedics from North East Ambulance Service NHS Foundation Trust (NEAS). The survey questions can be found in appendix C.

1.3.3.1 Sample and recruitment

A web link to the survey was sent by email to members of the CoP, along with promotion of the survey in the CoP newsletter (28/09/16 and 17/10/16). The survey was open for six weeks between 08/09/16 and 23/10/16. CoP members were targeted as they work in pre-hospital care across a range of settings and geographical locations in the UK. CoP and non-CoP paramedics were also invited by advertising the survey on social media (Twitter and Facebook). Two NHS ambulance trusts (East of England Ambulance Service NHS Trust (EEAST) and NEAS) also promoted the survey through internal communications.

In order to maximise the survey response rate, incentives (£50 gift vouchers), were offered to a random selection of 10 CoP members who participated.

1.3.3.2 Data collection and analysis

The data were collected via the web based service SurveyMonkey and reported descriptively (frequencies and percentage frequencies). Free-text comments were subjected to a functional content analysis to generate mutually exclusive categories.

1.3.3.3 Ethics

This survey was completed voluntarily by CoP members and did not include any sensitive topics. Ethics committee approval for the survey was not required based on the NHS Health Research Authority criteria.

1.3.4 Results

Two hundred and seventy-one people started the survey. Thirty-nine responses were removed as they were blank and one was removed as the respondent was not a paramedic. The 231 respondents included are described below (table 1.3.1). The 12 respondents in non-paramedic roles included 10 qualified paramedics and two student paramedics. All participants included from this point will be referred to as paramedics. Two hundred and thirty-one paramedics equated to 2% of CoP members (College of Paramedics, 2016) and 1% of paramedics registered with the Health and Care Professions Council (HCPC) (Health and Care Professions Council, 2016).

1.3.4.1 Demographics

The characteristics of respondents included in the study are shown in table 1.3.1.

Thirty-six respondents (16%) indicated that their main role did not involve working for an NHS ambulance trust. These respondents were distributed across the UK and worked in roles including Helicopter Emergency Medical Services (HEMS), private ambulance services and universities.

Table 1.3.1 Characteristics of survey respondents included in the study	
Gender	**n (%)**
Male	165 (71%)
Female	66 (29%)
Age	
18-20	2 (1%)
21-29	61 (27%)
30-39	76 (33%)
40-49	65 (28%)
50-59	26 (11%)
60+	1 (<1%)
Length of service in pre-hospital care	
<2 years	27 (12%)
3-5 years	40 (17%)
6-10 years	55 (24%)
11-20 years	76 (33%)
>20 years	33 (14%)
Current role	
Paramedic	134 (58%)
Specialist Paramedic	30 (13%)
Advanced Paramedic	15 (6%)
Consultant Paramedic	6 (3%)
Other Paramedic	34 (15%)
Non-Paramedic	12 (5%)
Highest level of education relevant to role	
IHCD Paramedic (Certificate of Higher Education)	53 (23%)
FdSc	56 (24%)
BSc	63 (27%)
Postgraduate (PGCert, PGDip, Masters)	57 (25%)
Doctorate	2 (1%)
NHS Ambulance Employer	
East Midlands Ambulance Service NHS Trust (EMAS)	18 (9%)

East of England Ambulance Service NHS Trust (EEAST)	38 (19%)
London Ambulance Service NHS Trust (LAS)	8 (4%)
National Ambulance Service (Ireland)	1 (<1%)
North East Ambulance Service NHS Foundation Trust (NEAS)	32 (16%)
North West Ambulance Service NHS Trust (NWAS)	10 (5%)
Northern Ireland Ambulance Service Health & Social Care Trust (NIAS)	6 (3%)
Scottish Ambulance Service (SAS)	13 (7%)
South Central Ambulance Service NHS Foundation Trust (SCAS)	7 (4%)
South East Coast Ambulance Service NHS Foundation Trust (SECAMB)	18 (9%)
South West Ambulance Service NHS Foundation Trust (SWAST)	15 (8%)
Welsh Ambulance Service NHS Trust (WAST)	4 (2%)
West Midlands Ambulance Service NHS Foundation Trust (WMAS)	13 (7%)
Yorkshire Ambulance Service NHS Trust (YAS)	12 (6%)

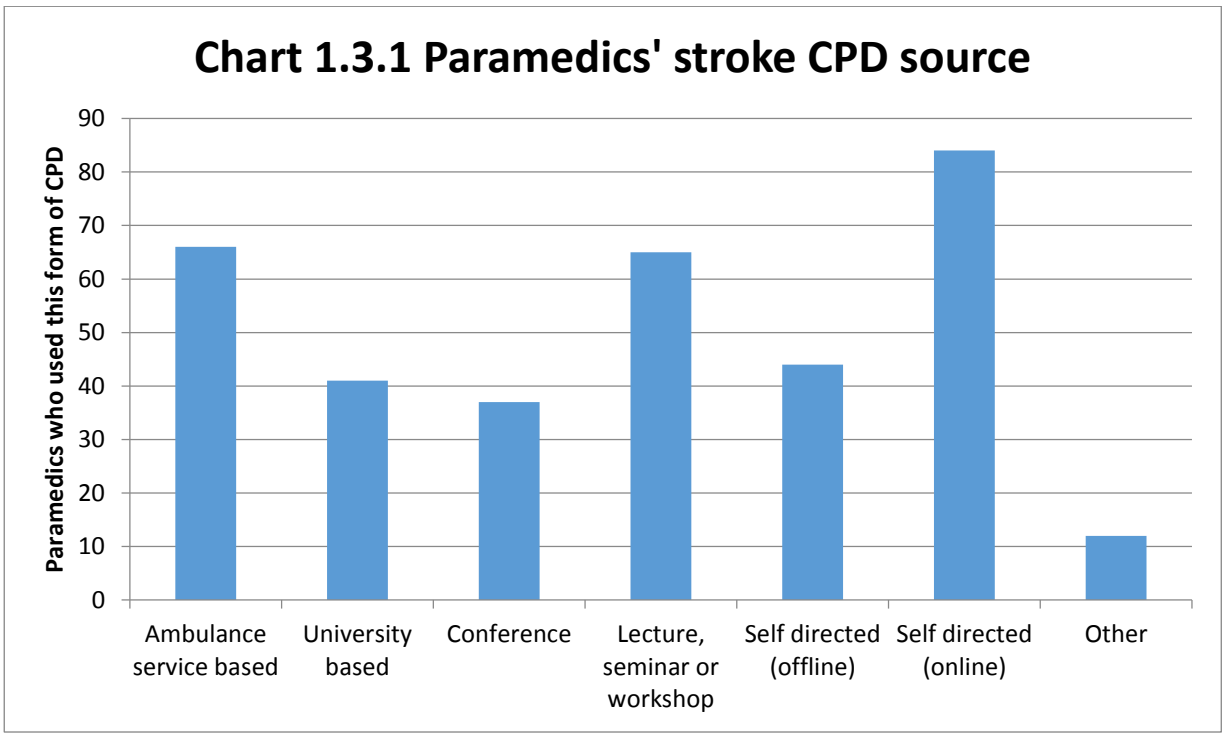
1.3.4.2 Stroke training and continuing professional development

Eighty-three respondents (36%) rated their initial pre-registration stroke training as inadequate, 144 (62%) as adequate and 4 (2%) rated it as excessive.

One hundred and eighty-two (82% from 223 answers) respondents indicated they would like more training on pre-hospital stroke care, 26 (12%) thought they did not need more training and 15 (7%) were unsure. When asked whether paramedics as a group needed more stroke training, 174/223 (78%) replied yes, 26 (12%) replied no and 23 (10%) were unsure.

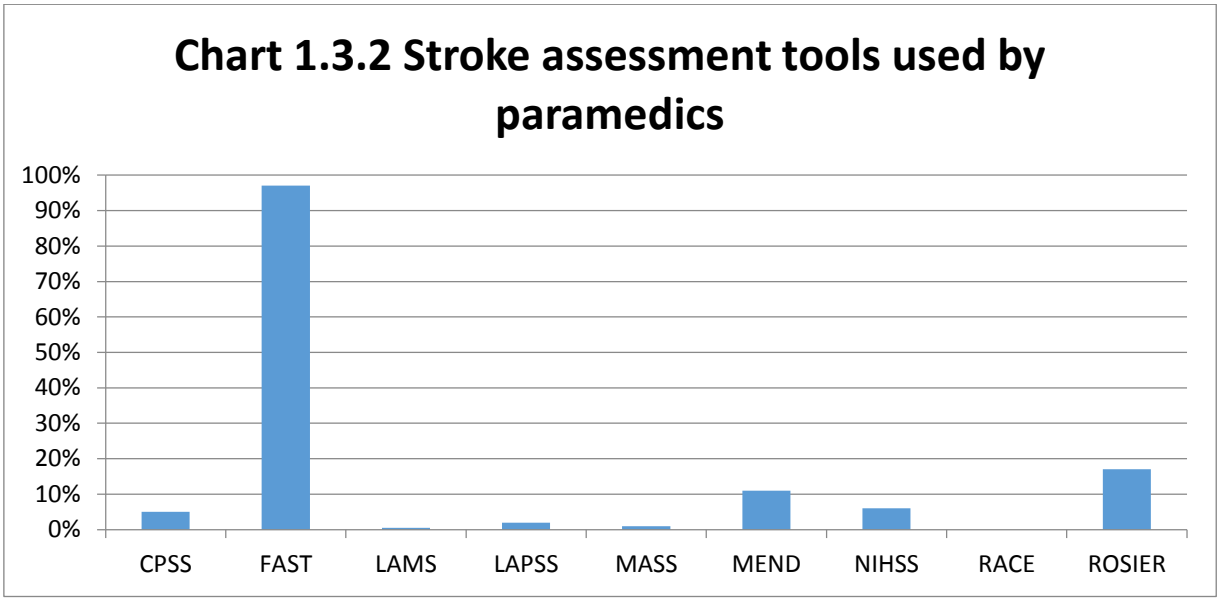
One hundred and twenty-eight (55%) respondents supplied comments when asked about what type of stroke training they would like to receive in the future. The main themes within the responses were improved assessment of suspected stroke patients; delivery of training by experts who can expand on later stages of acute stroke care; updates on pre-hospital stroke research and recognition of patients with atypical strokes such as FAST-ve and posterior circulation stroke.

One hundred and forty-three (64% from 223 answers) respondents indicated they had completed some stroke Continuing Professional Development (CPD) since qualifying (chart 1.3.1). The majority of the 'other' CPD related to research study based training. The median stroke-related CPD completed in the previous 12 months was 3 hours (IQR 1-7).



1.3.4.3 Stroke assessment tools

The tools used to assess patients with suspected stroke are displayed in chart 1.3.2. Most (n=209/216, 97%) respondents indicated they used FAST. Other stroke assessment tools were used infrequently (Cincinnati Pre-hospital Stroke Scale (CPSS) (Kothari *et al.*, 1999), Los Angeles Pre-hospital Stroke Screen (LAPSS) (Kidwell *et al.*, 2000), Melbourne Ambulance Stroke Screen (MASS) (Bray *et al.*, 2005), Miami Emergency Neurological Deficit (MEND) (Brotons *et al.*, 2012), National Institutes of Health Stroke Scale (NIHSS) (Brott *et al.*, 1989), Recognition of Stroke in the Emergency Room (ROSIER) (Fothergill *et al.*, 2013)) or not at all (Los Angeles Motor Scale (LAMS) (Llanes *et al.*, 2004), Rapid Arterial oCclusion Evaluation (RACE) (Perez de la Ossa *et al.*, 2014)).



1.3.4.4 Stroke compared to other time critical conditions

Three questions compared stroke with other time critical conditions (sepsis, ST segment elevation myocardial infarction (STEMI) and major trauma) with answers in the form of 5 point Likert scales. Answers were scored with 1 being the least confident/influence/change and 5 being the most. Responses to these three questions have been ordered using weighted averages.

Respondents were asked to rate how confident they felt dealing with patients with the time critical conditions. In ascending order of confidence the average responses were major trauma (3.74); stroke (4.14); sepsis (4.25); STEMI (4.30). See chart 1.3.3 for more detail.

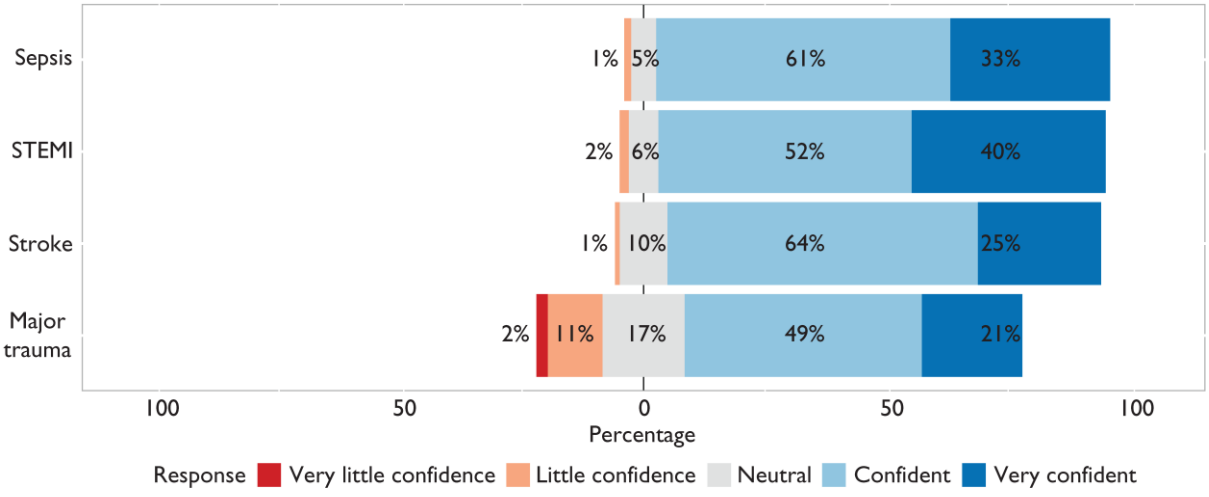


Chart 1.3.3 How respondents rated their confidence dealing with time critical conditions

Respondents were asked to what extent they thought pre-hospital actions influenced patient outcomes. In ascending order of influence the average responses were stroke (4.37); sepsis (4.49); major trauma (4.69); STEMI (4.81). See chart 1.3.4 for more detail.

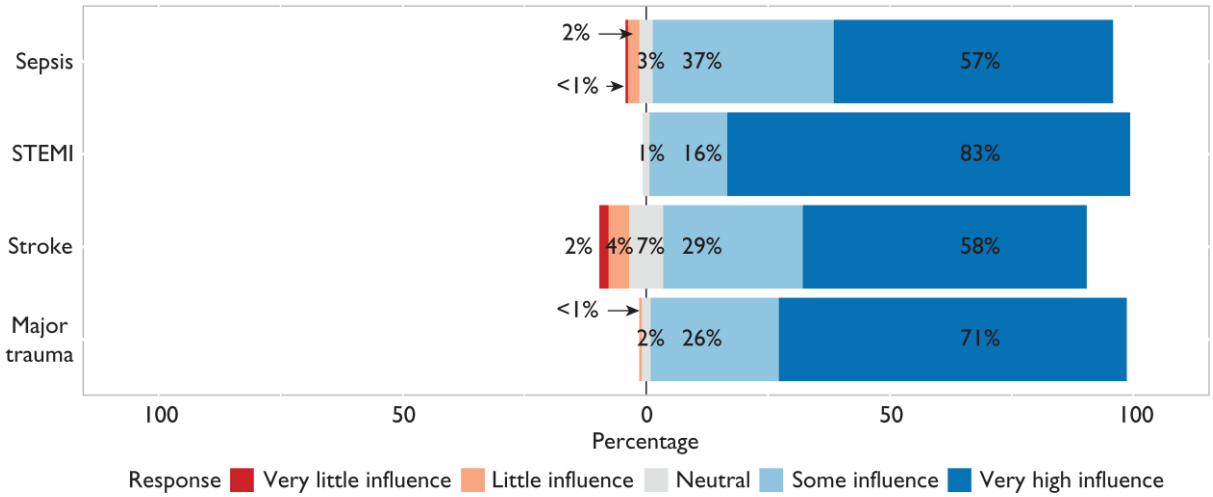


Chart 1.3.4 To what extent do you think pre-hospital actions influence patients' outcome

Respondents were asked how they thought pre-hospital care for the conditions had changed over their careers. In ascending order of improvement the average responses were stroke (3.97); STEMI (4.43); major trauma (4.47); sepsis (4.60). See chart 1.3.5 for more detail.

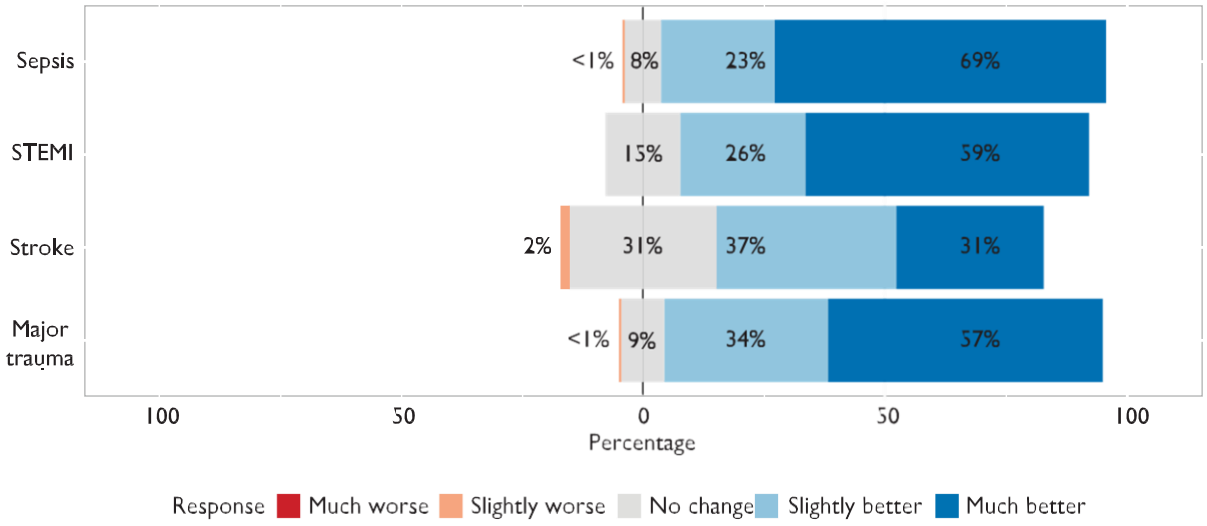


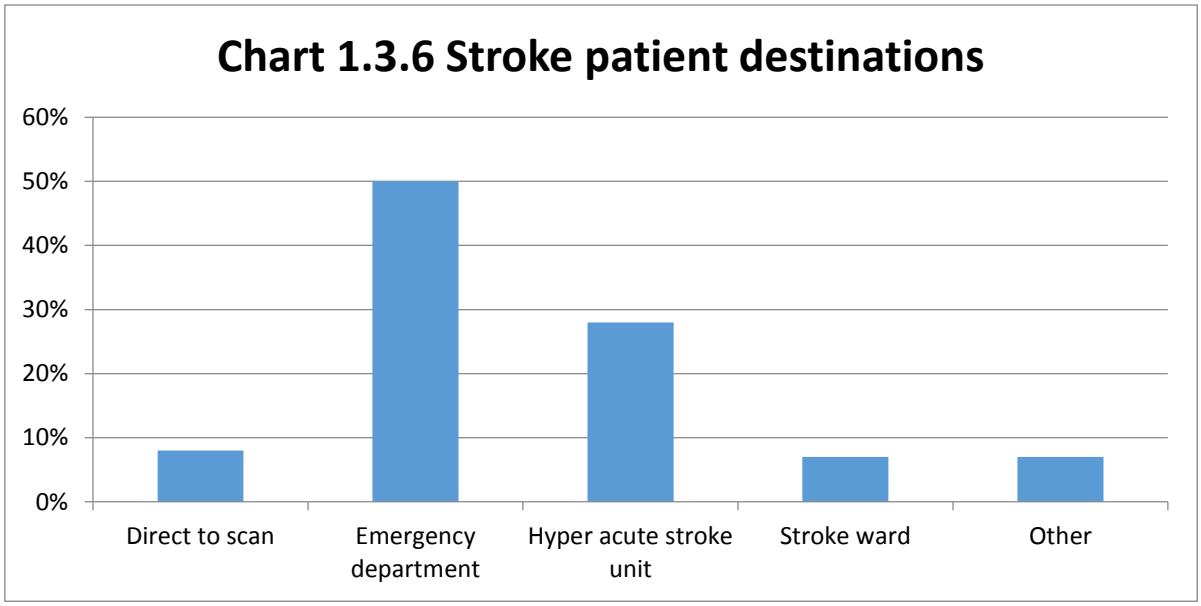
Chart 1.3.5 How do you think pre-hospital care has changed over the course of your career

1.3.4.5 Stroke transport

The responses to where most stroke patients were conveyed in their region are shown in chart 1.3.6. The most common destination for suspected stroke patients was the ED.

Fifty-nine (29% of 213 answers) respondents reported their destination could change depending on the time or day of the week.

Sixteen (8%) respondents reported access to telemedicine for stroke patients. Those who expanded upon this answer defined their access as being able to telephone either stroke teams at hospital or senior paramedics for advice.



The majority (n=197, 92%) of respondents thought that feedback on suspected stroke patients would be useful, but most (n=158, 74%) reported that they did not receive any. Forty-nine (23%) respondents indicated they received informal feedback, only 3% (n=6) reported they received feedback in a formal manner.

One hundred and forty-four (68%) respondents routinely performed an electrocardiogram (ECG) on suspected stroke patients, 16 (8%) reported only if the patient had chest pain and 53 (25%) reported that they would not routinely perform an ECG.

1.3.4.6 Transient Ischaemic Attacks

When asked whether they had TIA referral pathways in their region 94 (45% from 208 respondents) said yes. Fifty-two (25%) had access to TIA clinics in their region. Fifty-eight (28%) reported administering aspirin and 6 (3%) used other antiplatelet agents to treat patients with suspected TIA. Ninety-eight (47%) respondents reported using the ABCD2 (Johnston *et al.*, 2007) score for TIA risk stratification. ABCD2 was the only TIA risk tool used.

1.3.4.7 Stroke general questions

Respondents were asked about the current timeframe for thrombolysis in stroke patients which is a maximum of 4.5 hours. Twelve (6%) thought <2.5 hours, 28 (13%) <3.5 hours, 126 (61%) <4.5 hours and 42 (20%) <5.5 hours. One hundred and six (51%) respondents indicated they had heard of intra-arterial thrombectomy. Respondents thought stroke accounted for 5% (IQR 3-10) of their workload.

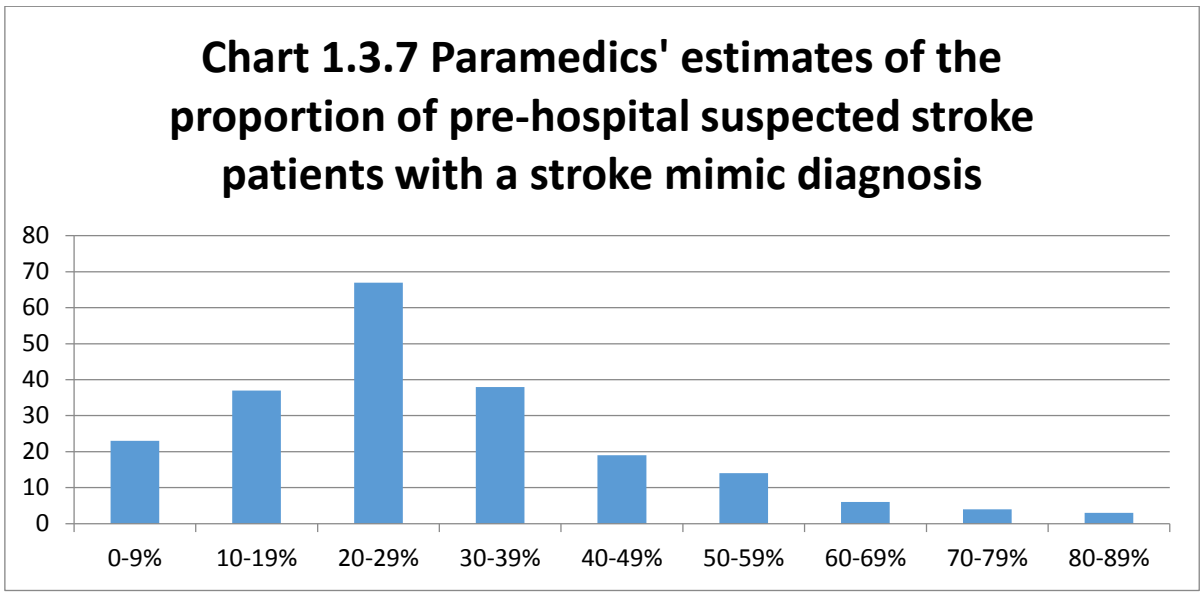
Forty-three individuals (20%) reported being involved in the following pre-hospital stroke studies: Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial 2 (RIGHT2) (Bath *et al.*, 2016) (n=30, 70%); Paramedic Acute Stroke Treatment Assessment (PASTA) (Shaw *et al.*, 2016) (n=11, 26%); Transient Ischaemic Attack 999 Emergency Referral (TIER) (Rees *et al.*, 2018) (n=3, 7%) and others (n=5, 12%).

At the end of the survey respondents were given the chance to comment on any aspect of pre-hospital stroke care. The main themes that emerged from 46 respondents' comments were a desire to improve the care they provided, concern over geographical variability and recognition of the time critical nature of pre-hospital stroke care.

1.3.4.8 Stroke mimics

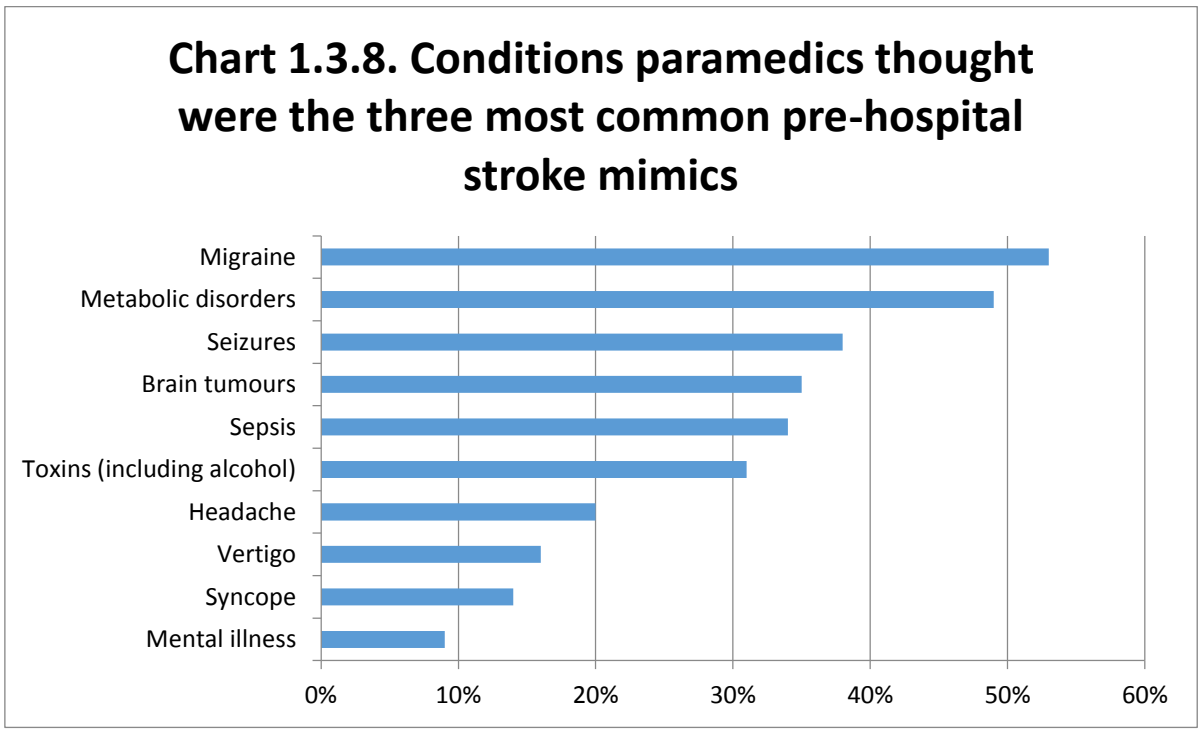
The majority (n=138, 65%) had heard of the term 'stroke mimics'. Overall 183 (86%) identified the correct definition which was stated as *"Where a patient appears to be having a stroke but their symptoms are due to a different condition*".

Respondents tended to give a conservative estimate of the proportion of suspected stroke patients transported to hospital by ambulance that were later given a SM diagnosis (chart 1.3.7).



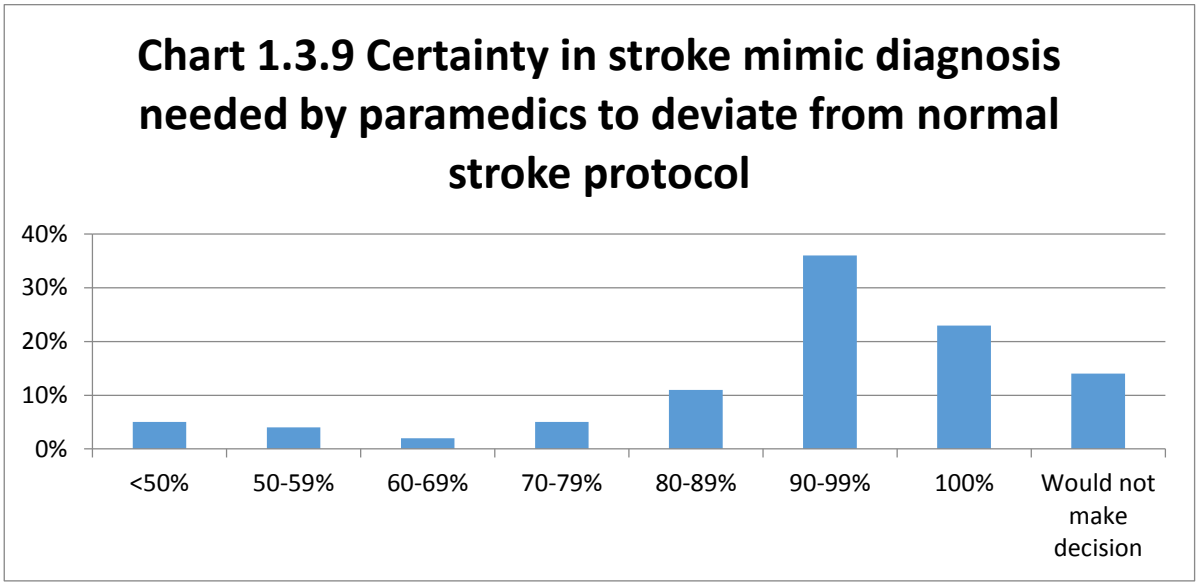
Respondents were asked which three conditions, out of ten suggestions were the most common pre-hospital SM (chart 1.3.8). The most common responses were migraine and metabolic disorders.

Respondents were asked if they thought a score to calculate the probability of a SM causing suspected stroke symptoms would be useful in pre-hospital care. One hundred and thirty-seven (65% from 211 answers) respondents thought that this would be useful, 30 (14%) thought it would not be useful and 44 (21%) were unsure. If a score was developed, the majority (n=154, 73%) preferred an electronic tool, which could be built into an existing electronic patient record system as opposed to a stand-alone application.



The survey asked how acceptable it would be for paramedics to treat a suspected stroke (FAST+ve) patient differently, based on a test indicating a high probability that the patient's symptoms were due to a SM condition e.g. transport to the ED as opposed to HASU: 24% thought that this was unacceptable; 27% were neutral; 49% thought this was acceptable.

Chart 1.3.9 shows that most respondents would need to be 90-99% certain that a patient was a SM, in order to deviate from their normal stroke protocol.



Respondents were asked for comments about pre-hospital identification and treatment of SM. The main themes were the potential risks for both patients and the staff making the SM diagnosis, and the need for organisational support if this type of decision was to be made.

1.3.5 Discussion

The results of this survey are a snapshot of paramedics' views about pre-hospital stroke care and SM. This is the first time a UK national survey of this type has been reported.

1.3.5.1 Pre-hospital workforce

Data were collected from paramedics with a range of roles, lengths of service, training and geographical locations in the UK. The respondents' demographics were similar to the HCPC register data, although the current sample was slightly younger. There were large numbers of respondents from two NHS ambulance trusts (EEAST and NEAS) which may have influenced the results based on their local practices. Half of respondents had qualified through a university. Based on these findings, and the low response rate, it is impossible to claim these results are representative of all paramedics and findings and conclusions should be interpreted accordingly.

1.3.5.2 Stroke training and continuing professional development

Although a small percentage (11%) had completed no stroke related CPD in the past year, the majority of respondents were in favour of more stroke related training. Stroke could be added to mandatory paramedic refresher training but would be in competition with multiple other training needs within limited time. Online learning was frequently used and has benefits for a geographically dispersed workforce such as paramedics. Providing opportunities for paramedics to undertake CPD which focuses on identified areas of interest such as assessment of suspected stroke patients and atypical strokes, or uses multi-disciplinary teams to deliver training, could encourage people to complete more stroke related training. Courses delivering this type of content report positive feedback (Haran *et al.*, 2016).

1.3.5.3 Stroke assessment, treatment and transport

FAST was the most commonly used stroke assessment tool and continues to be supported by national recommendations (Intercollegiate Stroke Working Party, 2016) (p34). A recent review (Rudd *et al.*, 2016a) reported that the FAST is supported by the most clinical evidence and has the best balance of characteristics, in terms of sensitivity and simplicity, for NHS stroke services. Despite being developed for ED use, and a clinical trial showing no additional value (Fothergill *et al.*, 2013), ROSIER was the second most frequently used stroke

assessment tool. MEND (Brotons *et al.*, 2012) was the third most frequently used assessment, largely due to use in one ambulance trust (SWAST).

For suspected stroke patients transported to hospital there were differences in pathways across the UK which are further complicated by variations based upon day and/or time. In addition there were variations in the destinations within the hospital.

There is little evidence that any standard pre-hospital interventions, beyond identification and rapid transport with pre-alert, positively affect stroke patient outcomes (Fassbender *et al.*, 2013; Puolakka *et al.*, 2016). Even standard observations such as ECGs, which 68% of respondents reported routinely performing on all stroke patients, have been questioned as they may delay transport (Munro *et al.*, 2018).

Most respondents received no feedback on stroke patients, but the majority would like feedback. Feedback on diagnosis would aid paramedics in reflecting on their decision making and actions. Feedback to paramedics about stroke patients has been shown to be beneficial (Choi *et al.*, 2014; Pollard and Black, 2015) in terms of promoting reflection and improving practice.

1.3.5.4 Stroke compared to other time critical conditions

When stroke was compared with other time critical conditions, paramedics felt more confident dealing with sepsis or STEMI than stroke, and less confident dealing with major trauma. This may be due to the low exposure to major trauma compared to the other conditions.

Respondents thought that pre-hospital stroke care had the least influence on outcome, and had improved the least over their career, out of the four conditions included in the study. The recent interest in sepsis, developments in regional trauma and STEMI care and the ability of paramedics to provide interventions perceived as beneficial in trauma, sepsis and STEMI may all contribute to the lack of perceived pre-hospital development of, and influence on patient outcomes in stroke care.

1.3.5.5 Research and developing treatments

Stroke consistently appears in priority setting exercises for pre-hospital research (National Ambulance Service Medical Directors, 2014) (p3) (Evans *et al.*, 2009). Previous research has shown that paramedics are keen to be involved in stroke related studies (Ankolekar *et al.*,

2014). Despite the fact that there were two large pre-hospital stroke studies recruiting (PASTA, RIGHT2), only 20% of respondents reported involvement in pre-hospital stroke research. This could be due to lack of opportunity, lack of desire to participate, lack of incentives, perceptions of research being an additional responsibility and other factors (Burges Watson *et al.*, 2012). This means that there should be enthusiasm from ambulance services and from paramedics to engage with research into pre-hospital SM identification however the low rate of participation in current studies and the many barriers to paramedic participation need to be considered.

Just over half (51%) of respondents were aware of intra-arterial thrombectomy. This is an emerging treatment for LVO strokes (McMeekin *et al.*, 2017). Pre-hospital input will be important, in terms of patient identification and bypass to specialist centres, for this treatment (Perez de la Ossa *et al.*, 2016).

1.3.5.6 Stroke mimics

As stroke services centralise, similar to STEMI care and regional trauma centres, awareness of, and potential paramedic identification of SM becomes more relevant due to the importance of pre-hospital redirection. A third of respondents had not heard of SM, which highlights a potential need for further education.

The literature review in chapter 1.2 showed that around a quarter of patients with suspected stroke were SM and that the most frequently reported SM diagnoses were seizure, syncope, sepsis, migraine and brain tumours. Data from the survey showed that most paramedics' perception of the frequency of SM was correct and that respondents were aware of the common SM.

Two thirds of respondents thought a SM prediction tool could be useful but when asked about how acceptable this would be in practice respondents were less sure. If a tool was to be used in practice then it would need to instil a high degree of confidence in the results i.e. have high specificity. Narrative data around SM identification showed concern over the risks to patients and the possible consequences for staff making clinical decisions based upon a SM tool. These concerns were identified as a point for discussion within the focus groups.

1.3.5.7 Limitations

Despite communications from the CoP, regular promotion through social media and the incentive of a prize draw, the number of completed surveys was low. Due to the diverse paramedic population it is impossible to calculate an exact response rate which is a potential source of bias in this study. It is difficult to judge the representativeness of the sample due to the lack of national paramedic demographic data, but the survey does include responses from the majority of trusts, roles and locations where paramedics work. Two trusts were disproportionately represented which may have biased the results based on their local practices. The proportion of respondents with postgraduate qualifications was high and may not be representative of the wider population of paramedics. This study relied on voluntary participation, self-reported data and respondents' perceptions which have inherent limitations.

1.3.6 Conclusions

This study reports a survey of UK paramedics' views about the stroke care that they provide. Conclusions are limited by the low number of responses. Assessment of suspected stroke patients is recognised as an important skill by paramedics and an area where many would like further training. Respondents' current practice varied in terms of the stroke assessment tools used and where suspected stroke patients were admitted. Many were aware of SM, but underestimated their frequency. A SM identification tool would be useful if it allowed SM patients to be directed to appropriate care, but it would need to have a high level of specificity and not adversely impact on time to treatment for true stroke patients.

1.3.7 Summary

This chapter demonstrated that most paramedics were aware of SM, had some comprehension of what proportion of suspected stroke cases they comprised and what the common SM were. Paramedics appear to be open to the idea of a SM identification tool. The data reported here, particularly the need for high levels of certainty, will influence the development of the SM identification tool. The next chapter describes the creation of a dataset describing suspected stroke patients attended by a UK regional ambulance service linked with the final diagnoses of these patients. This dataset will be used, in conjunction with the findings of the systematic review described in chapter 1.2 and the survey of paramedics reported in this chapter, to develop the initial SM identification tool.

Chapter 1.4 Pre-hospital suspected stroke in North East England

1.4.1 Introduction

The systematic review (chapter 1.2) showed that 27% of pre-hospital suspected strokes were SM. However, it reported a combination of pre-hospital studies, none of which were based in the UK or used FAST. The survey of paramedics in chapter 1.3 found that FAST was the most commonly used stroke identification tool in the UK. As the aim of this project was to develop a SM identification tool in the UK, data were sought from a UK ambulance service using FAST. This chapter describes suspected stroke patients identified by a regional UK ambulance service using FAST, linked to the final hospital diagnosis in order to establish the SM rate and describe the characteristics of the SM population.

1.4.2 Chapter aims

This chapter has three aims:

1. To describe the pre-hospital suspected stroke population.
2. To establish the SM rate in a UK ambulance service.
3. To describe the causes of SM conditions.

1.4.3 Methods

A retrospective cohort study used individual pre-hospital patient data to establish the suspected stroke population. This was then linked with hospital based patient diagnoses to report the number of stroke patients who were correctly identified in the pre-hospital setting, this allowed the SM rate to be calculated and the characteristics of SM patients to be reported.

1.4.3.1 Study setting

NEAS is the regional ambulance service provider for ~2 million people in North East England. The stroke identification tool used in NEAS is the FAST, which was developed in the North East as described in chapter 1.1. Research involving NEAS has previously reported SM rates of 22-23% (Harbison *et al.*, 2003; Nor *et al.*, 2004). These figures are over 10 years old and based upon a newly established redirection service. In order to inform this thesis, more recent data were needed.

1.4.3.2 Pre-hospital data collection

Retrospective data were obtained from NEAS using a clinical database query created by the NEAS Informatics team. This report included data on NEAS patients with a recorded suspicion of stroke defined as any recording of stroke or TIA in the chief complaint or clinical impression sections of the NEAS patient care record. The report included demographic data; physiological observations; presenting signs and symptoms; Past Medical History (PMH) and free-text comments.

Forty-eight variables (listed below) were extracted from the pre-hospital data based on the findings of the systematic review (chapter 1.2) and availability within the NEAS records.

- Impression
- Age
- Gender
- Blood sugar (BM)
- Glasgow Coma Scale (GCS)
- Heart Rate
- Pain (0-10)
- Peripheral Oxygen Saturation (SaO2)
- Respiratory Rate
- Systolic Blood Pressure (SBP)
- Diastolic Blood Pressure (DBP)
- Temperature
- Pulse regularity
- PMH Angina
- PMH Heart failure
- PMH High Cholesterol
- PMH Hypertension
- PMH MI
- PMH Diabetes
- PMH Smoking
- PMH Epilepsy
- PMH Stroke
- PMH TIA
- PMH Migraine
- PMH Alcohol misuse
- Dizziness
- General weakness
- Nausea or vomiting
- Syncope
- Chest pain
- Abnormal Gait
- Arm weakness
- Confusion
- Facial droop or weakness
- Floppy
- Headache
- Leg weakness
- Neck Stiffness
- Seizures
- Speech symptoms
- Tremors
- Unconscious
- FAST+ve
- Alcohol/Drug use reported
- AF
- Eye issues
- Visual disturbances
- Altered Sensation

1.4.3.3 Pre-hospital data format

Information on patients seen by NEAS was recorded using an Electronic Patient Record Form (EPRF). An example EPRF is included in appendix D. The EPRF contained information recorded in two formats.

The first was structured data. Structured data included frequently used fields, usually with pre-set answers, such as gender, FAST and the ABC based primary survey. Structured data also included commonly recorded identifiers recorded using free-text including name, date of birth or address.

Structured data were normally recorded in a positive fashion, i.e. if a patient had chest pain then the chest pain box was ticked. Data could also be recorded in a negative fashion. If a paramedic wished to document the absence of a sign or symptom the box could be ticked twice which recorded a pertinent negative, i.e. if a patient with chest pain reported that they have not vomited then this would be recorded as a pertinent negative to show that it has been considered. Pertinent negative data were included in the data requested.

The second data format was free-text or narrative. This was recorded through a free-text comments field in the EPRF. This was used to expand on the structured data, provide a narrative history of events and decisions taken and to include data that did not fit in the structured data sections. These data were typically not used for audit or reporting purposes due to the wide variability in what, and how, data were recorded.

Some factors relevant to differentiating strokes and SM identified in the systematic review were not part of the EPRF structured data, therefore in order to report a complete description of the pre-hospital observations, free-text data were included in the database query.

A protocol was written for collecting the free-text data to reduce the variability inherent in reporting the narrative information (appendix E). These data were extracted using a standardised checklist with the 48 variables taken from the list above. Data collection was performed by a single researcher (GM).

Due to awareness of the problems inherent in narrative data extraction and interpretation, and the use of a single researcher to extract all the data, the reliability of the free-text data extraction was examined. In order to examine the intra-rater reliability of the data extraction process the process was repeated on a randomly chosen sample of 60 cases 14 months after the initial data extraction. The inter-rater reliability of the free-text data extraction was also tested by a second researcher extracting data from a randomly chosen sample of 60 cases using the data collection protocol and data extraction sheet. The second researcher was a senior paramedic within NEAS with a similar level of experience to the author. Data were analysed for agreement using Cohen's kappa.

1.4.3.4 Identifying pre-hospital stroke patients

There were two fields in the EPRF where paramedics record their suspicion of stroke: 'Chief complaint' and 'Impression'.

Chief complaint was documented early in the EPRF as a single choice from a pre-specified list. Chief complaint included very broad common categories such as chest pain, falls, stroke/TIA and traumatic injuries and summarised the patient's stated primary problem.

Impression was documented at the end of the EPRF and represented the paramedic's provisional conclusions and the conditions identified. Impression could include multiple conditions and was also selected from pre-specified options.

Impression including stroke was selected for the cohort inclusion criteria as it represented the paramedic's suspicion of stroke as the main problem as opposed to the much broader, patient based chief complaint.

1.4.3.5 Timeframe

The final dataset included 36 months of data covering 01/06/2013 to 31/05/2016. This timeframe was chosen based on the availability of a complete retrospective dataset with all the NEAS data available in an electronic format.

1.4.3.6 Pre-hospital data inclusion/exclusion criteria

Inclusion

- NEAS contact between 01/06/2013 and 31/05/2016
- Adult (18+) patients with a recorded impression including 'stroke'
- Patient transported to hospital

Exclusion

- Inter-hospital transfers
- Admission other than by NEAS emergency ambulance (e.g. helicopter, self-presentation)

1.4.3.7 Linking pre-hospital data with patient diagnoses

Pre-hospital data cannot be used in isolation when seeking to establish any measure of diagnostic accuracy, including the SM rate, as it does not include a final diagnosis. In order to report on the accuracy of pre-hospital stroke identification, and identify factors differentiating stroke and SM, the pre-hospital dataset was linked to hospital sourced diagnostic data.

An application was made to the Sentinel Stroke National Audit Programme (SSNAP) to obtain data on suspected stroke patients attended by NEAS across the North East in order to create a regional dataset. SSNAP audits stroke care in England, Wales and Northern Ireland through the collection of individual stroke patient data and reports on care from the acute phase through to six month outcomes. SSNAP is entered by the local specialist stroke teams and then cross referenced with the Office for National Statistics (ONS), therefore all patients in SSNAP are confirmed stroke. The application to SSNAP was eventually withdrawn due to the extended timeframe involved and concerns with the completeness of the SSNAP data pertinent to this thesis. However, with suitable information governance processes in place individual services were able to share their SSNAP data with other NHS organisations (i.e. NEAS). Consequently, acute NHS trusts with stroke services in the North East were approached directly for access to their data.

The first acute trust approached was Northumbria Healthcare NHS Foundation Trust (NHCT). NHCT is an NHS acute trust covering Northumbria and North Tyneside which is the northern

part of the area covered by NEAS. NHCT provides care for over 500,000 people across the region. NHCT stroke care was provided at three hospitals which then centralised into one site, the Northumbria Specialist Emergency Care Hospital (NSECH) at Cramlington. NSECH admitted 1,008 confirmed stroke patients in 2016/17. NHCT consistently performs well in the SSNAP audit in criteria relevant to this work such as case ascertainment where it scored 90%+ (North of England SCN, Apr16-Mar17, (RCP, 2017b)).

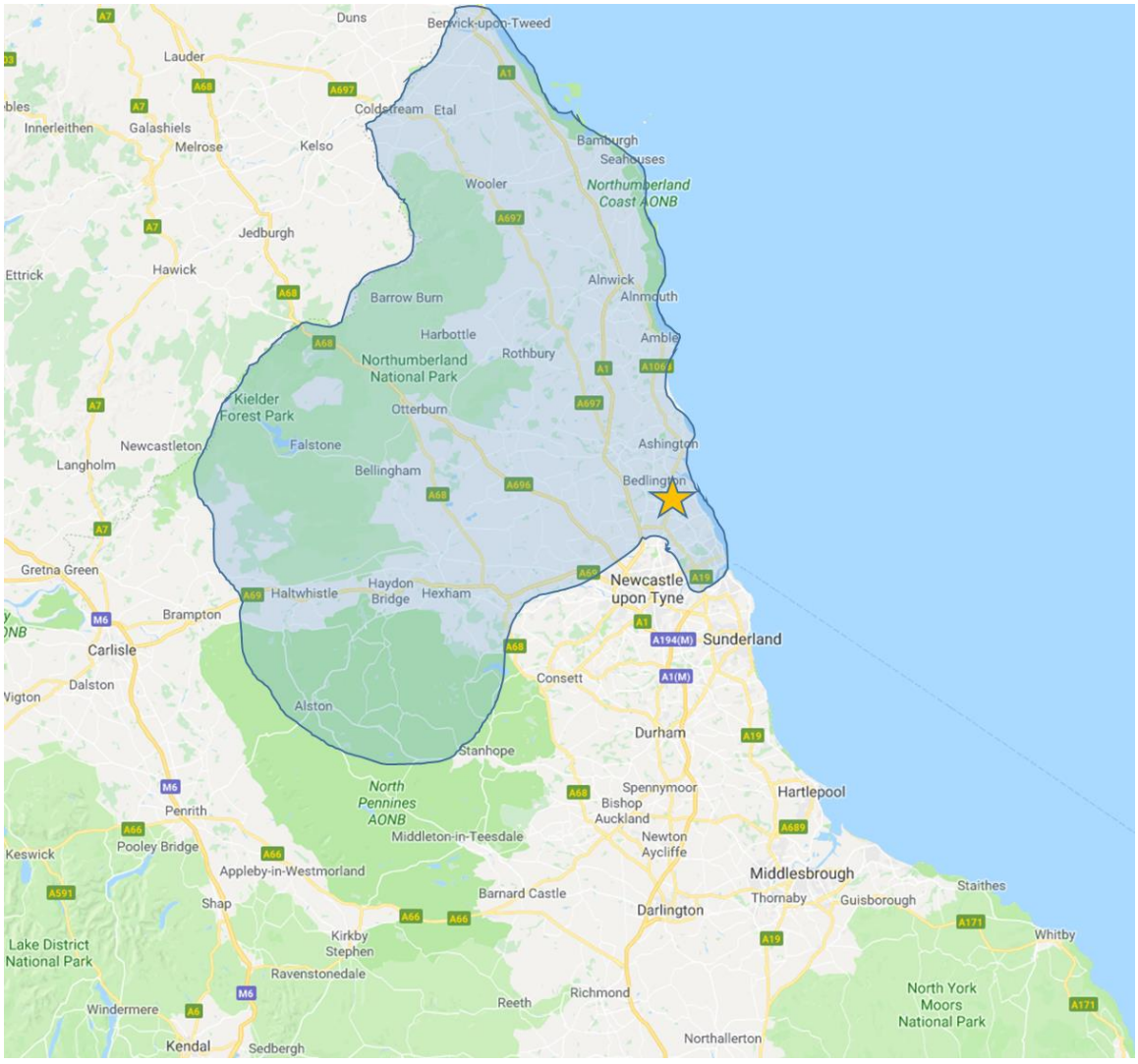


Figure 1.4.1 Map of the North East showing NHCT approximate catchment area

Linkage of NEAS suspected stroke patients with NHCT diagnoses provided robust data for developing a SM identification tool which is described in the next chapter. Other acute trusts in the North East were also approached about sharing their stroke data in order to expand the dataset and allow further development of the SM tool which is described in parts 2 and 3 of this thesis.

1.4.3.8 Data linkage methods

Patient diagnoses data were collected from NHCT to determine the stroke or SM status of patients admitted as suspected stroke by NEAS. These data were collected in two stages:

1. NHCT SSNAP data was used to identify patients recorded as stroke.
2. All patients not matched with SSNAP were sought in NHCT patient administration system records to determine their final diagnoses.

1.4.3.9 Data linkage – stage 1

NEAS and NHCT data were linked using a protocol (appendix F). Patient identifiers such as name and date of birth were removed from the NHCT SSNAP data for information governance reasons, so data were linked with NEAS data using ambulance call number. If ambulance call number was not recorded in the NHCT SSNAP data, probabilistic matching was performed using admission timestamp, gender and age.

Patients with a positive match between NEAS records and NHCT SSNAP were recorded as stroke (see figure 1.4.2 below). Patients with a potential match (admission time >20 minutes difference, missing age, etc.) were re-examined with access to the original NEAS EPRF to look for additional data.

The reliability of the data linkage process was checked by an independent researcher repeating the process on a sample of 60 randomly selected records. The independent researcher was based within NEAS with a similar knowledge of clinical record systems and access to the same resources. Inter-rater reliability is reported using Cohen's kappa as a measure of agreement.

1.4.3.10 Data linkage – stage 2

NEAS suspected stroke patients who could not be linked with the NHCT SSNAP data were then sought in other NHCT records. This process involved using identifiers within the NEAS data (name, age, date of admission) to identify the patient in the NHCT Hospital Episode Statistics (HES) records and establish their discharge diagnoses. HES is the central standard data warehouse that has collected data on all hospital attendances in England since 1989. HES is used to guide NHS and governmental decisions on healthcare in England and is a reliable source of standardised information.

Discharge diagnoses were categorised using International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) codes. ICD-10 codes are standard codes used to record diagnoses.

NEAS suspected stroke patients who were unable to be linked with SSNAP or confidently linked with NHCT HES records were assumed to be SM. Confidently linked SM patients and the assumed SM patients were compared for any demographic differences.

Figure 1.4.2 summarises the data linking and adjudication process.

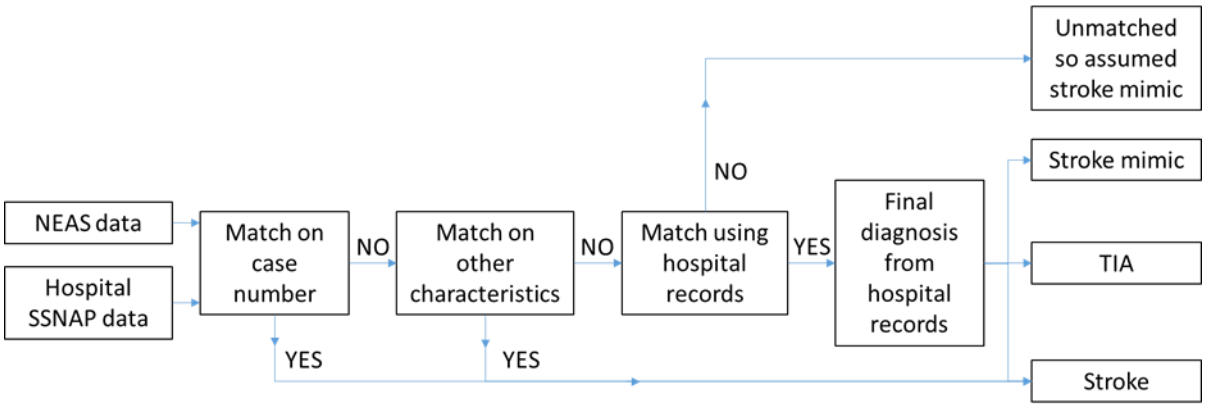


Figure 1.4.2 Data linking process for determining final diagnosis of suspected stroke patients admitted by NEAS

1.4.3.11 Patient diagnoses definitions

For this study stroke was defined as inclusion in the SSNAP dataset or as hospital recorded diagnosis including ICD-10 codes I61 (nontraumatic intracerebral haemorrhage), I63 (cerebral infarction) and I64 (stroke, not specified as haemorrhage or infarction). This is based on the definition of stroke used by SSNAP, which also provides a high degree of confidence about complete data capture within SSNAP because of cross-referencing with Hospital Episode Statistics (HES).

Patients with a diagnosis of TIA are not included in SSNAP. TIA is defined as "*stroke symptoms and signs that resolve within 24 hours*" (National Institute for Health and Care Excellence, 2017) which means differentiating stroke and TIA can be challenging in the pre-hospital setting where total patient contact time is often short. The decision was taken to group TIA with stroke due to the similar presentation and pre-hospital response. TIA has been grouped with stroke in other pre-hospital studies (Fothergill *et al.*, 2013; Brandler *et*

al., 2015). This grouping also allowed suspected stroke patients to be reported using a dichotomous outcome measure (stroke/TIA versus SM). TIA patients were identified by ICD-10 codes G458 (other transient cerebral ischaemic attacks and related syndromes) and G459 (transient cerebral ischaemic attack, unspecified). All other ICD-10 codes were reported as SM.

1.4.3.12 Data analysis

All data were collated in Microsoft Excel and analysed in IBM SPSS Statistics v23.

Continuous variables, such as means for physiological variables, were compared using the independent samples t-tests. Independent categorical variables, such as the presence of FAST symptoms, were compared using the chi-squared test. Inter and intra-rater reliability of the data matching and extraction processes were examined using Cohen's kappa.

1.4.3.13 Missing data

Listwise deletion, or complete-case analysis, was used to explore the impact of missing data (Haukoos and Newgard, 2007). Listwise deletion involves removing all cases with any missing data.

1.4.3.14 Approvals and ethics

This case identification and data collection study was conducted as a service evaluation based upon the HRA definition (Health Research Authority, 2017). NEAS provided R&D project registration, and Caldicott approvals were secured from NEAS and NHCT to share the necessary data.

1.4.4 Results - Establishing the SM rate and describing SM conditions

1.4.4.1 NEAS and NHCT data

Across NEAS there were 24,764 suspected stroke cases between 01/06/2013 and 31/05/2016.

1,552 cases (6%) had a null value for destination. These cases were excluded from any further analysis due to the small numbers and the difficulty in establishing the final diagnosis in the absence of a destination. These missing location cases may have been: data entry errors; patients with reports completed by rapid response vehicles who handed the patient on to a second crew to transport; or the patient may not have travelled to hospital.

The NEAS suspected stroke patients were filtered to identify patients admitted to NHCT. The remaining patients were filtered based on paramedic impression then duplicates and inter-hospital transfers were removed. There were no patients <18 years old. This resulted in 1,742 suspected stroke cases being included. The filtering process is shown in figure 1.4.3.

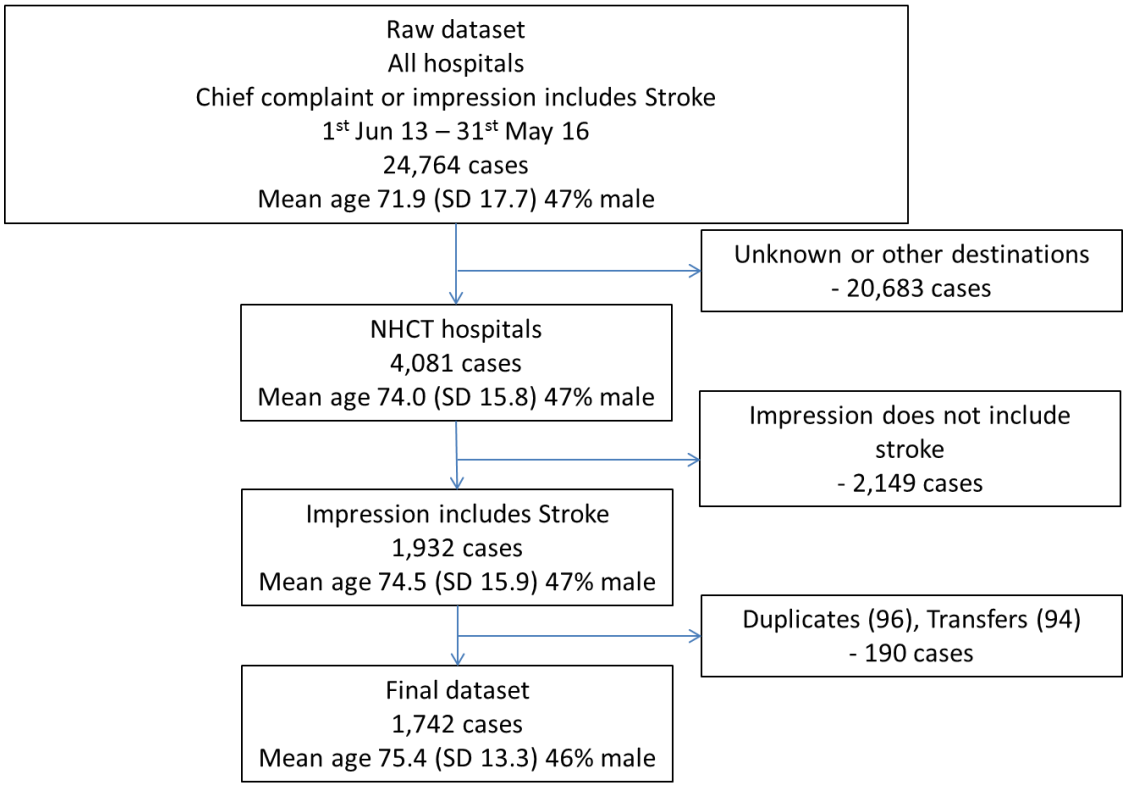


Figure 1.4.3 NEAS suspected stroke patients filtered from raw data to NHCT dataset

1.4.4.2 Patient diagnosis data collection – stage 1

Initial matching with NHCT SSNAP data positively identified 875 (50%) NEAS suspected stroke patients as strokes.

1.4.4.3 Inter-rater reliability check of stroke identification

The agreement for the data linkage process was 58/60 (97%). Cohen's kappa = 0.933 (95% CI 0.843-1) which is very good agreement (Landis and Koch, 1977). The cases where disagreement was reported were discussed to arrive at a consensus. One disagreement was due to an error in the recording of patient gender in the NEAS data. The second disagreement was due to incorrect data matching by the independent checker.

1.4.4.4 Patient diagnosis data collection – stage 2

From the total cohort of 1,742 suspected stroke patients 875 (50%) were identified as stroke patients using SSNAP. The remaining 867 suspected stroke patients who were not positively matched in the SSNAP data were searched for within the NHCT HES records.

- 84 patients were identified as TIA (ICD-10 codes G458 and G459) based on NHCT HES records.
- 74 patients were identified as stroke based on NHCT HES records including diagnostic codes I61, I63 and I64.
- 560 patients had a SM ICD-10 diagnosis.
- 149 patients were unable to be linked with either SSNAP or HES. These patients were all assumed to be SM.

Combining these figures results in 1,033 (59%) stroke patients and 709 (41%) SM patients.

1.4.4.5 Final diagnoses

The final diagnoses of NEAS suspected stroke patients (n=1,742) was 59% stroke (n=1,033, 949 strokes plus 84 TIAs) and 41% SM (n=709). This achieves the second aim of this chapter which was to report the SM rate in a UK ambulance service. The process of establishing the final diagnoses for NEAS suspected stroke patients is summarised in figure 1.4.4.

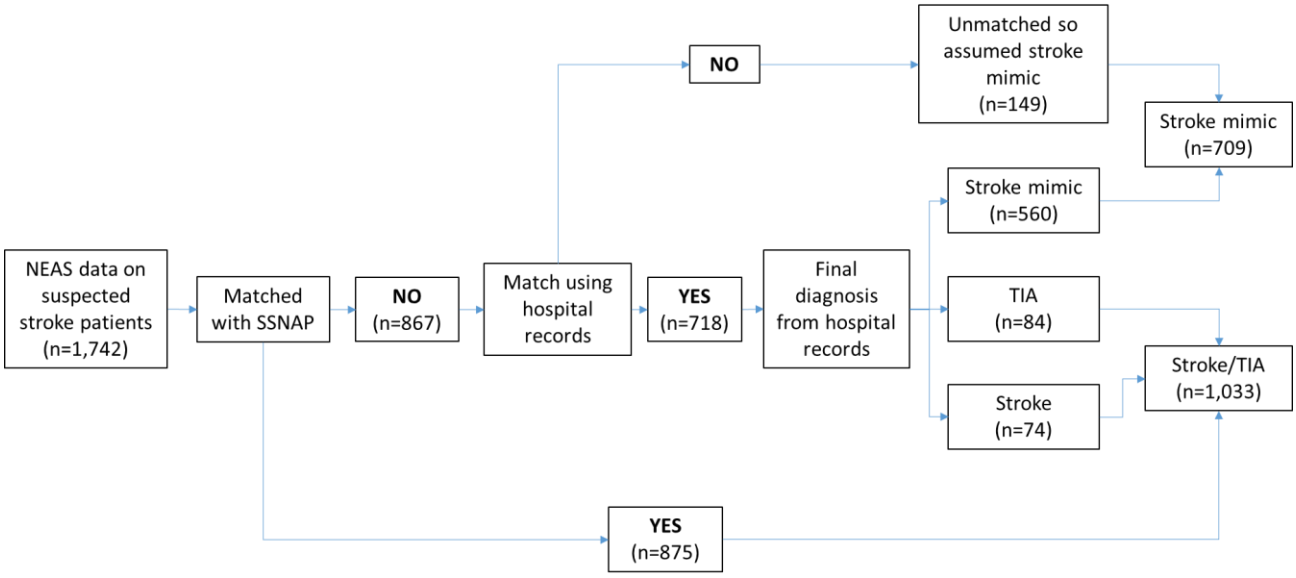


Figure 1.4.4 Data linking process showing final diagnoses of suspected stroke patients admitted by NEAS

1.4.4.6 SM diagnoses

SM patients were identified (n=709) by either confirmed non-stroke diagnoses (n=560, 79%, including any ICD-10 code other than I61, I63, I64 or TIA codes G458 and 459) in NHCT HES system or assumed (n=149, 21%) based on inability to match with either SSNAP or HES.

The patients assumed to be SM (n=149) were compared with the patients with a confirmed SM diagnosis as shown in table 1.4.1.

Table 1.4.1 Comparison of patients with confirmed SM diagnosis versus assumed SM diagnosis

Diagnosis	Age (mean, SD)	Gender (% Male)
Confirmed (n=560)	74.2 (14.5)	39
Assumed (n=149)	68.6 (16.4)	41

The two groups of SM patients were significantly different in age (independent samples t-test, $p<0.001$) but not significantly different in gender (chi square test, $p=0.608$).

One hundred and seventy-two different ICD-10 diagnostic codes were recorded for the 560 patients with a confirmed SM diagnosis. The ICD-10 based SM diagnoses are displayed in table 1.4.2.

Table 1.4.2 Most frequent ICD-10 diagnoses recorded for SM patients		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
N390	Urinary tract infection, site not specified	38 (7%)
R568	Convulsions, not elsewhere classified	37 (7%)
R55X	Syncope and collapse	30 (5%)
R298	Other symptoms and signs involving the nervous and musculoskeletal systems	25 (4%)
G409	Epilepsy, unspecified	24 (4%)
J181	Lobar pneumonia, unspecified organism	22 (4%)
G439	Migraine, unspecified	14 (3%)
G510	Bell's palsy	14 (3%)
R296	Repeated falls	11 (2%)
R478	Other speech disturbances	11 (2%)
E162	Hypoglycemia, unspecified	10 (2%)
F059	Delirium due to known physiological condition	10 (2%)
I620	Nontraumatic subdural hemorrhage	10 (2%)
J22X	Unspecified acute lower respiratory infection	10 (2%)
G819	Hemiplegia, unspecified	9 (2%)
I609	Nontraumatic subarachnoid hemorrhage, unspecified	9 (2%)
C793	Secondary malignant neoplasm of brain and cerebral meninges	8 (1%)
N179	Acute kidney failure, unspecified	8 (1%)
A419	Sepsis, unspecified organism	7 (1%)
G442	Tension-type headache	7 (1%)
I629	Nontraumatic intracranial hemorrhage, unspecified	6 (1%)
I951	Orthostatic hypotension	6 (1%)
R410	Disorientation, unspecified	6 (1%)
R471	Dysarthria and anarthria	6 (1%)
Other	Other conditions with less than 1% (n=6) prevalence	222 (40%)

The ICD-10 codes were summarised using CCS codes (as used earlier in chapter 1.2). The most frequent SM diagnoses represented using level 2 CCS codes are shown in table 1.4.3.

Table 1.4.3 NHCT SM diagnoses displayed using level 2 CCS codes		
CCS level 2 code	**CCS description**	**Number (%) of patients**
6.4	Epilepsy; convulsions	70 (13%)
6.9	Other nervous system disorders	50 (9%)
10.1	Diseases of the urinary system	48 (9%)
13.8	Other connective tissue disease	38 (7%)
17.1	Symptoms; signs; and ill-defined conditions	36 (6%)
8.1	Respiratory infections	32 (6%)
7.3	Cerebrovascular disease	31 (6%)
6.5	Headache; including migraine	26 (5%)
5.4	Delirium dementia and amnestic and other cognitive disorders	18 (3%)
7.2	Diseases of the heart	15 (3%)
3.4	Other endocrine disorders	11 (2%)
6.3	Paralysis	10 (2%)
7.4	Diseases of arteries; arterioles; and capillaries	10 (2%)
8.8	Other lower respiratory disease	10 (2%)
1.1	Bacterial infection	9 (2%)
2.12	Secondary malignancies	8 (1%)
6.8	Ear conditions	8 (1%)
3.8	Fluid and electrolyte disorders	7 (1%)
Unknown	Unknown	7 (1%)
2.11	Cancer; other primary	6 (1%)
2.3	Cancer of bronchus; lung	6 (1%)
16.4	Intracranial injury	6 (1%)
16.8	Superficial injury; contusion	6 (1%)
Other	Other conditions with less than 1% (n=6) prevalence	92 (16%)

The CCS codes were combined into level 1 CCS codes to show broader clinical groupings as shown in table 1.4.4.

Table 1.4.4 NHCT SM diagnoses displayed using level 1 CCS codes		
CCS1 code	**CCS description**	**Number (%) of patients**
1	Infectious and parasitic diseases	11 (2%)
2	Neoplasms	34 (6%)
3	Endocrine; nutritional; and metabolic diseases and immunity disorders	22 (4%)
4	Diseases of the blood and blood-forming organs	2 (<1%)
5	Mental Illness	26 (5%)
6	Diseases of the nervous system and sense organs	175 (31%)
7	Diseases of the circulatory system	59 (11%)
8	Diseases of the respiratory system	53 (9%)
9	Diseases of the digestive system	11 (2%)
10	Diseases of the genitourinary system	48 (9%)
11	Complications of pregnancy; childbirth; and the puerperium	1 (<1%)
12	Diseases of the skin and subcutaneous tissue	3 (1%)
13	Diseases of the musculoskeletal system and connective tissue	44 (8%)
16	Injury and poisoning	26 (5%)
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	38 (7%)
18	Residual codes; unclassified; all E codes [259. and 260.]	7 (1%)

The NHCT SM diagnoses are graphically displayed in figure 1.4.5 with figure 1.2.3 from the systematic review repeated below for comparison.

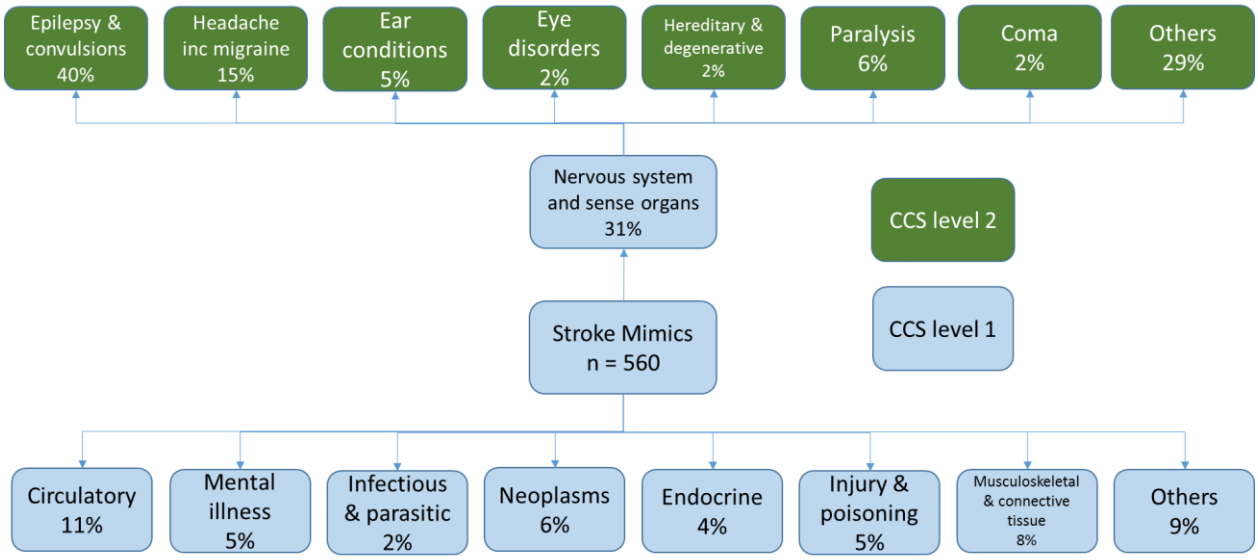


Figure 1.4.5 NHCT SM diagnoses summarised using CCS codes

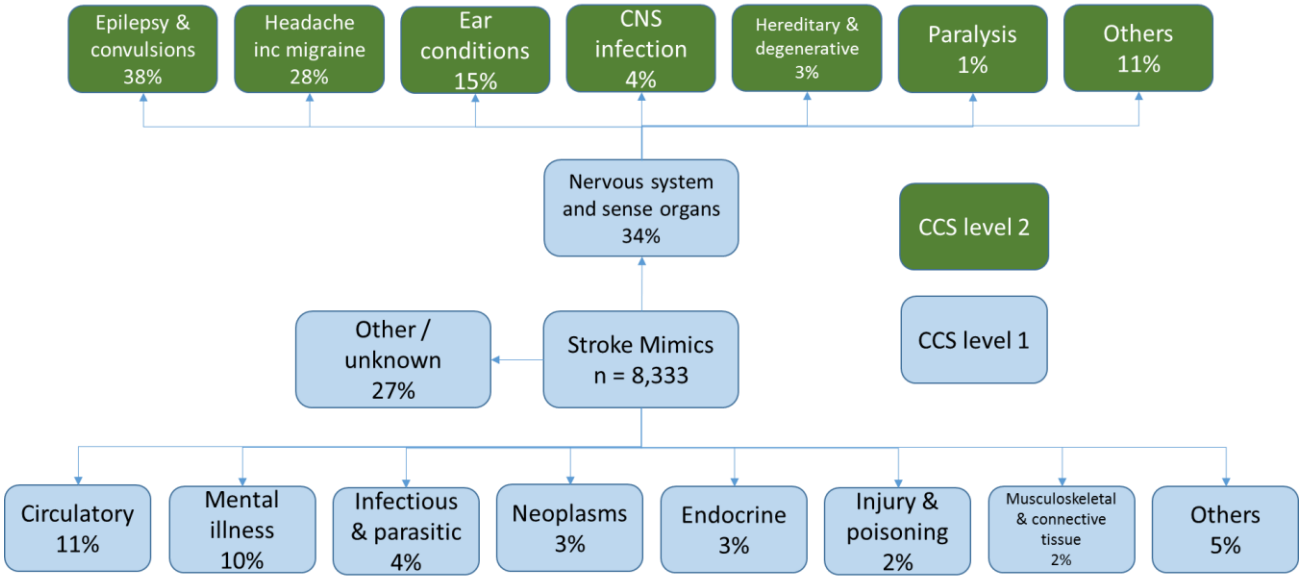


Figure 1.2.3 Taxonomy of SM using CCS codes (repeated from chapter 1.2)

1.4.5 Results – describing the suspected stroke population

The suspected stroke population is described based on NEAS data combined with the stroke or SM diagnoses supplied by NHCT.

1.4.5.1 Structured and free-text data

The data presented includes 11,435 data points extracted from the NEAS EPRFs (n=1,742 patients). This includes a combination of structured and free-text data to present a complete picture of the information documented on suspected stroke patients. Figure 1.4.6 shows that 50% of the data were only recorded in a structured format, 30% of the data were duplicated (recorded in both structured and free-text format) and 19% of the data were only recorded in a free-text format. Two characteristics were only found in the free-text data (eye issues and altered sensation) and one characteristic (visual disturbances) was a combination of a free-text and a structured characteristic. If these three characteristics were removed, then the free-text data would account for 15% additional data as opposed to 19%. All data reported in the thesis are based on combined structured and free-text data.

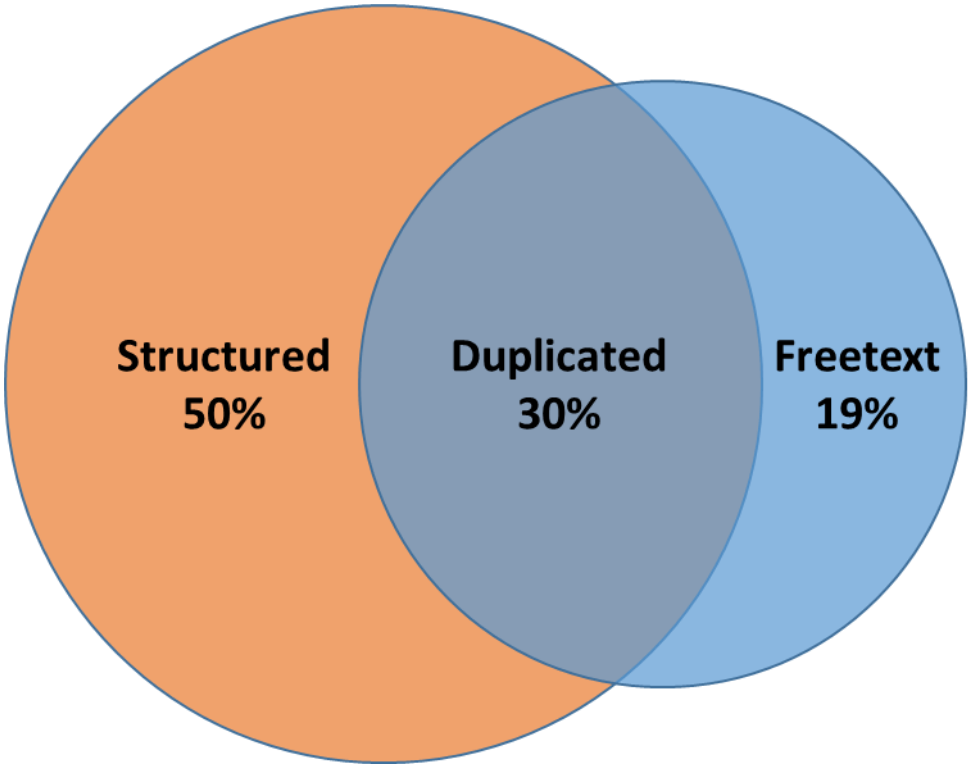


Figure 1.4.6 Venn diagram showing source of data extracted from NEAS EPRF

1.4.5.2 Reliability of free-text data extraction

The results of the intra-rater testing was a Cohen's kappa intra-rater reliability coefficient of 0.936 (95% CI 0.911-0.961, p<0.001) which indicates near perfect agreement (Landis and Koch, 1977). The results of the inter-rater testing was a Cohen's kappa reliability coefficient of 0.752 (95% CI 0.707-0.797, p<0.001) which indicates substantial agreement.

A sample of 20 data points where there was disagreement were examined in detail. In 14 (70%) it was obvious on re-examination why there was disagreement as the data was recorded in the EPRF but one of the data extractors had failed to record it. In 4 cases (20%) there was vagueness in the free-text data which had been interpreted in different ways. In 2 cases (10%) a data point had been recorded by the data extractor with no obvious justification or source within the EPRF.

1.4.5.3 Pertinent negative data

The medical history and observational data extracted from NEAS included pertinent negative data (observations marked as not present, i.e. patient did not have chest pain).

Pertinent negative data was not included in the analysis for three reasons:

- The frequency with which negative data was recorded. Positive characteristics were recorded twice as frequently as negative characteristics.
- Positive and negative features were sometimes recorded due to a changes in a patient's condition. Inclusion of both would have introduced a cancelling effect and created unusual associations during the regression analysis.
- The absence of positive documentation of a characteristic in clinical practice does usually reflect an assumption that the patient did not have the characteristic.

Based on these reasons the decision was made to focus on positively recorded characteristics.

1.4.5.4 Missing data

Listwise deletion was used to explore the impact of removing patients with missing data (all patients without a full set of demographic and physiological observations were excluded). If this was applied the remaining dataset would include 882 (51% of total) patients. This

reduced dataset would include 541 (58%) stroke patients and 341 (42%) SM, the mean age would be 74.7 (SD 13.3) and 50% of patients would be male so the overall demographics and SM rate would be similar to the complete dataset. As the aim was to describe the suspected stroke population, which includes which data is present or missing, and listwise deletion would have severely reduced the sample size and the power of the study, all the data were included.

Examination of the missing data led to the assumption that the missing data were randomly distributed apart from SBP and DBP which are linked. Pain and temperature were the main observations that were not documented. If patients with missing pain and/or temperature values were excluded then the remaining dataset included 958 (55%) patients. The remaining patients had all the other physiological observations documented in >95% of cases.

A small number (n=3, 0.2%) of patients had no physiological data recorded at all. One of these patients had no other data apart from age and gender recorded. All three of these patients were classed as SM. A slightly larger group (n=10, 0.6%) of patients had no physiological observations apart from pulse regularity recorded. Three of these patients were classed as SM and seven had a stroke diagnosis. The only missing demographic data was age in eight (0.5%) patients all of whom were recorded as adults. All of these patients had physiological and other observations documented and two were classed as SM and six received a stroke diagnosis.

1.4.5.5 Physiological observations data cleaning

The physiological data were checked for anomalous values before any analysis was conducted. GCS and pain were checked for values outside of the defined limits (GCS 3-15; pain 0-10). Other observations were checked for values outside of the reference ranges shown in table 1.4.5. If anomalous values were identified these were checked against the source data (NEAS EPRF). Values which were physiologically implausible (respiratory rate of 1, temperature of 18^{o}C) were removed. Entries which appeared to be data input errors (respiratory rates of 12, 12, 92, 12) were amended.

Table 1.4.5 Reference range for physiological observations and number of amended and deleted values		
Variable	**Range counted as plausible**	**Outcome**
BM	3-30	1 amendment
Heart rate	40-170	2 deleted, 2 amended
SAO2	75+	1 deleted, 3 amended
Respiratory rate	10-40	2 deleted, 4 amended
SBP	80-240	1 amended
DBP	40-150	1 amended
Temperature	34+	3 deleted, 4 amended

Where multiple observations were recorded on a single patient the mean of the values was calculated. The mean was used based on the assumption that patients' observations would not change dramatically in the short period of time that they were in the care of paramedics.

1.4.5.6 Stroke and SM population demographics

The demographics of the NHCT cohort are displayed below. 100% of patients had a gender recorded. Eight (0.5%) patients had no age documented but were recorded as adults so were included.

Table 1.4.6 Demographics of NEAS suspected stroke patients admitted to NHCT reported by discharge diagnosis				
	Total sample	**Stroke**	**SM**	**P value**
Number patients	1,742	1,033	709	-
Mean age (SD)	75.4 (13.3)	77.1 (11.6)	73.0 (15.1)	<0.001
Gender (% male)	46%	50%	41%	<0.001

The mean age for males in the NHCT cohort was 73.2 (stroke 74.2, SM 71.4). The mean age for females in the NHCT cohort was 77.3 (stroke 79.9, SM 74.1).

1.4.5.7 Paramedic documentation of clinical impression

Paramedic impression was examined to establish whether it related to final diagnosis. Impression was grouped into three distinct categories:

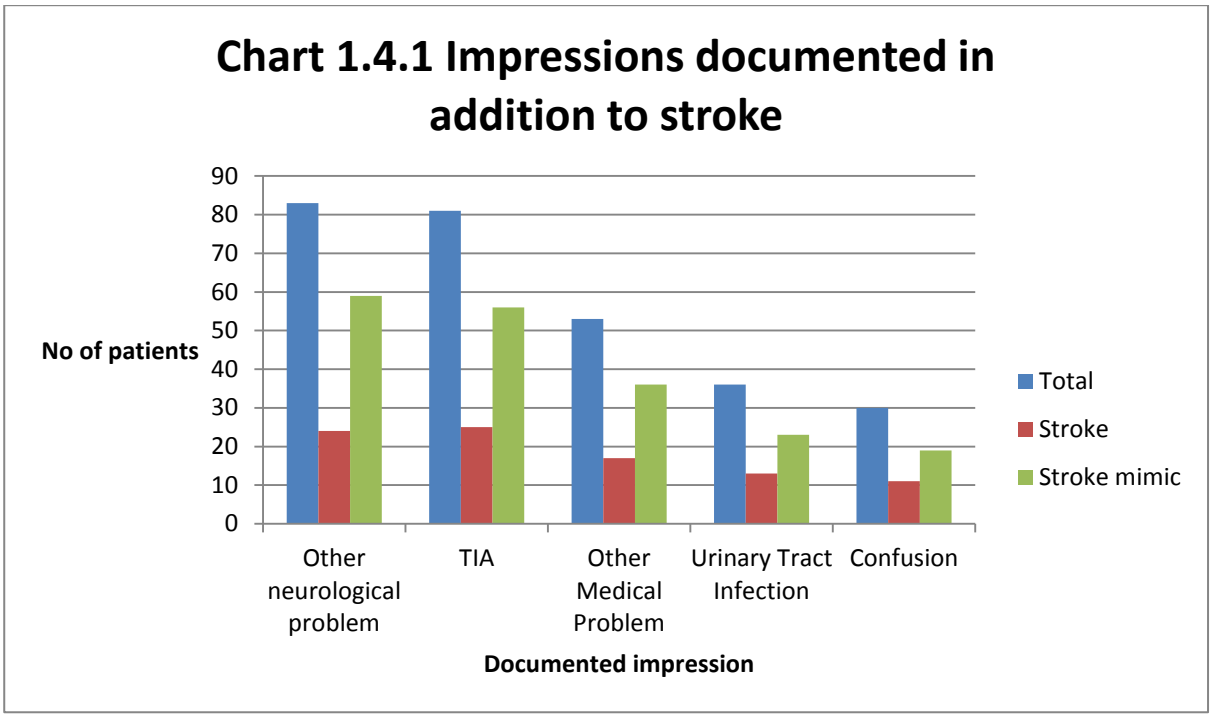
1. Stroke only = stroke as only suspected diagnosis.
2. Stroke and TIA = stroke and TIA documented as only diagnoses.
3. Stroke plus other = stroke included amongst multiple differential diagnoses.

These three categories of impression were then compared with final hospital diagnoses to see if there was any pattern.

Table 1.4.7 Paramedic impression and final diagnoses

Impression	Total patients	Stroke	SM
Stroke only	1353	881 (65%)	472 (35%)
Stroke and TIA	132	74 (56%)	58 (44%)
Stroke plus others	257	78 (30%)	179 (70%)

The stroke plus other impression category included stroke plus a median of 1 additional impression (range 1-7, IQR 1-2). Stroke patients with impression of 'stroke plus other' had 26 different impressions documented in addition to stroke. SM patients with impression 'stroke plus other' had 41 different impressions documented in addition to stroke. The 5 most common additional impressions are shown in chart 1.4.1. TIA reported below denotes stroke plus TIA plus at least one other impression being recorded.



1.4.5.8 Physiological observations

The physiological observations are displayed below.

Table 1.4.8 Physiological observations in NEAS data on suspected stroke patients admitted to NHCT reported by final diagnosis

Physiological observation	% of patients with observation documented	Stroke (mean, SD)	SM (mean, SD)	P value
BM (mmol/l)	95%	7.7 (2.7)	7.3 (2.4)	0.003
GCS	99%	13 (2.5)	13 (2.8)	0.038
Heart rate	99%	82 (18.8)	85 (20.3)	0.002
Irregular pulse	97%	25%	19%	0.001
Pain (0-10)	62%	0.3 (1.2)	0.5 (1.5)	0.023
SaO2	99%	96 (2.9)	95 (3.8)	0.102
Respiratory rate	99%	17 (3.1)	17 (3.4)	0.248
SBP (mmHg)	98%	160 (28.5)	153 (30.3)	<0.001
DBP (mmHg)	98%	89 (17.4)	87 (19.0)	0.013
Temperature (Celsius)	86%	36.4 (0.7)	36.6 (0.9)	0.001

1.4.5.9 Past medical history

The recording of relevant items of PMH are displayed below. These items were selected based on the systematic review (chapter 1.2), clinical input from the supervisory team and availability within the NEAS dataset.

Table 1.4.9 Past medical history of NEAS suspected stroke patients admitted to NHCT reported by final diagnosis

Medical History	Patients with condition (% of total patients)	Stroke (% of stroke patients with condition)	SM (% of SM patients with condition)	P value
Alcohol misuse	24 (1%)	8 (1%)	16 (2%)	0.009
Angina	148 (8%)	88 (9%)	60 (8%)	0.967
Diabetes	284 (16%)	178 (17%)	106 (15%)	0.206
Epilepsy	59 (3%)	17 (2%)	42 (6%)	<0.001
Heart failure	43 (2%)	35 (3%)	8 (1%)	0.003
High cholesterol	238 (14%)	146 (14%)	92 (13%)	0.490
Hypertension	518 (30%)	341 (33%)	177 (25%)	<0.001
MI	148 (8%)	96 (9%)	52 (7%)	0.150
Migraine	25 (1%)	8 (1%)	17 (2%)	0.005
Smoking	38 (2%)	24 (2%)	14 (2%)	0.624
Stroke	466 (27%)	247 (24%)	219 (31%)	0.001
TIA	270 (15%)	160 (15%)	110 (16%)	0.988

1.4.5.10 Clinical signs and symptoms

The signs and symptoms recorded by the paramedics are displayed below.

Table 1.4.10 NEAS observations on suspected stroke patients transported to NHCT reported by final diagnosis				
Observation	**Patients with observation (% of total)**	**Stroke (% of stroke patients with observation)**	**SM (% of SM patients with observation)**	**P value**
Abnormal gait	167 (10%)	110 (11%)	57 (8%)	0.069
AF	210 (12%)	153 (15%)	57 (8%)	<0.001
Alcohol/Drug use reported	38 (2%)	20 (2%)	18 (3%)	0.398
Altered Sensation (FT)*	132 (8%)	84 (8%)	48 (7%)	0.291
Arm weakness**	1074 (62%)	746 (72%)	328 (46%)	<0.001
Chest pain	16 (1%)	6 (1%)	10 (1%)	0.075
Confusion	497 (29%)	282 (27%)	215 (30%)	0.17
Dizziness	135 (8%)	81 (7%)	54 (8%)	0.863
Eye issues (FT)*	97 (6%)	72 (7%)	25 (4%)	0.002
Facial droop or weakness	922 (53%)	612 (59%)	310 (44%)	<0.001
FAST+ve***	900 (52%)	582 (56%)	318 (45%)	<0.001
Floppy	107 (6%)	71 (7%)	36 (5%)	0.125
General weakness	425 (24%)	234 (23%)	191 (27%)	0.041
Headache	354 (20%)	189 (18%)	165 (23%)	0.011
Leg weakness**	777 (45%)	564 (55%)	213 (30%)	>0.001
Nausea and vomiting****	205 (12%)	112 (11%)	93 (13%)	0.148
Neck Stiffness	23 (1%)	12 (1%)	11 (2%)	0.484
Seizures	71 (4%)	19 (2%)	52 (7%)	<0.001
Speech symptoms	1077 (62%)	700 (68%)	377 (53%)	<0.001
Syncope	16 (1%)	7 (1%)	9 (1%)	0.203
Tremors	50 (3%)	19 (2%)	31 (4%)	0.002

Table 1.4.10 NEAS observations on suspected stroke patients transported to NHCT reported by final diagnosis cont.

Observation	Patients with observation (% of total)	Stroke (% of stroke patients with observation)	SM (% of SM patients with observation)	P value
Unconscious***	129 (7%)	47 (5%)	82 (12%)	<0.001
Visual disturbances****	127 (7%)	73 (7%)	54 (8%)	0.665

*Altered sensation and eye issues are not documented in a structured fashion in the EPRF so these have been taken from the free-text data (indicated by FT). Altered sensation included descriptions such as tingling, pins and needles and strange sensations. Eye issues were recorded when signs related to eye movement or function were documented such as dysconjugate gaze or fixed stare.

**Limb weakness includes documented left, right or bilateral limb weakness.

***FAST+ve is reported when the FAST test is documented or completed in a structured format, not when individual FAST components are documented in isolation.

****Nausea and vomiting were documented separately but have been combined together in this analysis.

*****Unconscious includes any documented or reported episode.

******Visual disturbances were recorded when symptoms such as blurred or double vision were documented.

1.4.6 Discussion

This study describes linkage of clinical data between suspected stroke patients transported by a UK regional ambulance service and hospital records to establish the patients' final diagnoses. This allowed the true positive and false positive rates to be calculated for the pre-hospital diagnoses and the stroke and SM populations to be described. Based on this data the false positive (SM) rate in suspected stroke patients transported by NEAS to NHCT was 41%.

1.4.6.1 Establishing the sample data

The choice of NEAS as the location for this study was pragmatic but also informed by the history of pre-hospital stroke research within the area. This study builds on earlier work on pre-hospital stroke identification and redirection (Harbison *et al.*, 2003; Nor *et al.*, 2004), as well as more recent work exploring pre-hospital documentation of stroke symptoms (Rudd *et al.*, 2016a) and ongoing work on streamlining pre-hospital stroke pathways (Shaw *et al.*, 2016).

The local partnership with NHCT allowed confident reporting of patients' final diagnoses based upon hospital records which may not have been possible using either a regional or national data source. This method will serve as a template for expanding the dataset and involving additional hospital trusts to refine and validate a SM identification tool as described in chapter 1.0.

Linking pre-hospital data to hospital outcomes is of interest to ambulance services across the UK (Clark *et al.*, 2016; Duncan *et al.*, 2017). However, there are challenges with this process due to inconsistencies such as misspelling of names, missing data and differences in admission times recorded between ambulance and hospital datasets. The data linkage method was developed based on identifiers available within the pre-hospital and hospital datasets. The process for linking NEAS data to NHCT SSNAP was tested and showed a high level of agreement which demonstrated the reliability of the process. Similar methods have been used in other pre-hospital studies (Downing *et al.*, 2005; Mumma *et al.*, 2015) despite the acknowledged difficulties (Sanddal *et al.*, 2017). The stepwise process of using NHCT SSNAP data and then tracing unmatched patients in HES appears to have been largely successful as the number of additional stroke patients found in the HES data was small (n=74, 7% of total stroke patients). These patients may have been missed during the initial matching due to inconsistencies between NEAS and NHCT data, missing data within the NEAS EPRF or the patient having been missed off SSNAP (although the latter is unlikely due to the high case ascertainment rate within NHCT).

SSNAP and NHCT HES data were used as the reference standards for patient diagnoses. The choice of these reference standards was very important as they defined the diagnoses of the suspected stroke patients, and by extension the performance of any tests developed on

these data. The combination of SSNAP and HES patient diagnoses should be highly reliable and provide as close to a gold standard reference test as is practical for this type of study (Knottnerus *et al.*, 2002).

All diagnoses that are reported were based on retrospective analysis and therefore local clinical judgement as opposed to pre-defined diagnostic criteria. In an ideal world all patients included in this study would have undergone identical assessments and investigations and therefore all diagnoses would have been established using the same methods. As this work is based on clinical service data, this is acknowledged not to be the case. Patients that appeared to be SM, or with non-typical stroke symptoms, may have been assessed in a different manner to patients with more obvious stroke symptoms, in turn this may have influenced the final diagnosis. The impact of a standardised protocol for assessment of all suspected stroke patients would make an interesting area for further research.

Whilst the reference standard for stroke has been discussed above, the reference standard for TIA is less clearly defined. TIA is a hospital based diagnosis based on clinical information similar to stroke but often without neuroimaging evidence, so there may be more variability. In this thesis TIA is grouped with stroke based on the difficulties distinguishing the two conditions in the pre-hospital setting and due to the time related nature of TIA diagnosis. TIA has been defined in other studies as both stroke (Fothergill *et al.*, 2013; Brandler *et al.*, 2015) and SM (Barker *et al.*, 1984; Eichel *et al.*, 2013). If TIAs were completely excluded, then the SM rate increased to 43% whereas if TIA was classed as a SM then the SM rate increased to 46%. It would be very difficult to exclude TIA from pre-hospital records as it can be indistinguishable from stroke in the pre-hospital setting. Considering the data on paramedic impression presented in table 1.4.7, when paramedics included TIA in their impression the SM rate increased from 35% to 44%, therefore excluding TIA patients would exclude a large number of SM patients.

Data reported in this study were guided by the systematic review (chapter 1.2) and availability within the NEAS systems. The choice of impression as the inclusion criteria excluded some patients with a chief complaint of stroke/TIA, but as the study focussed on pre-hospital identification impression was more relevant as it represented the pre-hospital clinicians' provisional diagnosis.

1.4.6.2 Free-text data reliability

The inclusion of free-text data within this study was labour intensive, but was necessary when the limitations of the structured data were realised. Inclusion of the free-text data added 2,224 data points which would have been missed if the structured data were used in isolation. Extracting and interpreting free-text data raises issues around reliability due to the variability in how patient observations are documented by individual clinicians (John *et al.*, 2016).

Intra-rater reliability of the free-text data extraction showed near perfect agreement which demonstrates that the data extraction was performed consistently. Inter-rater reliability of the free-text data extraction revealed some differences in how the narrative data could be interpreted and that the free-text data were extracted in slightly different ways by the two data extractors. This would need to be accounted for in future work in this area with more than one researcher extracting data through a standard data extraction process and development of agreed definitions for potentially ambiguous data.

In order to achieve reliable free-text data extraction in future work a clear protocol would need to account for issues including the timing of documented observations (i.e. did the reporters witness the symptoms or were they reported by others) and the numerous ways in which similar observations can be documented, i.e. arm weakness; right/left sided weakness; limb weakness; lack of arm strength.

1.4.6.3 Missing data

There were varying amounts of missing data within the NEAS dataset. Demographic data were consistently documented. Physiological observations were largely (>95%) recorded apart from pain (62%) and temperature (86%). Other observations, including PMH and signs and symptoms, were assumed to be present if recorded and absent if not recorded therefore it was assumed there were no missing data in these fields. Patients with missing data were not excluded and missing data were not imputed as one of the aims of this study was to describe the suspected stroke population and this includes the completeness of the dataset. As it stands, the current data reflect the real-world documentation made by paramedics.

1.4.6.4 Suspected stroke population

Demographics in the form of mean age (suspected stroke 75.4, stroke 77.1, SM 73.0) and gender (suspected stroke 46% male, stroke 50% male, SM 41% male) were reported for patients in this study. Males had a lower mean age than females in all three categories.

These demographics are consistent with the chapter 1.2 which reported the demographics of pre-hospital stroke patients as 51% male with a mean age of 73 and SM patients as 42% male with a mean age of 67. The national stroke audit showed that the median age for stroke patients admitted to hospital was 77 years and 51% were male (RCP, 2017a)(pg 36).

The SM population are older than would be expected from the literature which may be due to the exclusion of patients under 18 years. The overall pattern in the data presented here is of SM patients being younger and more likely to be female than stroke patients, which is consistent with the literature review.

The population reported in this chapter was drawn from the catchment area of a single hospital trust (NHCT) so the demographics of the population covered by NHCT need to be considered. The area covered by NHCT includes eight medium sized towns and suburbs, but does not include central Newcastle, or another major city, therefore the population included in this study may not be generalizable to populations outside the NHCT catchment area. NHCT also covers a large amount of sparsely populated rural areas which again may limit generalisability.

Comparing the demographics of stroke patients reported here against recent figures from Manchester, London and similar areas across the UK (Ramsay *et al.*, 2015) the age of the NHCT patients was higher (NHCT 77.1 years vs 72.7-74.6 years), whereas the data on gender were similar (NHCT 50% male vs 48-51% male). Consequently, the demographics reported in this chapter are reasonably representative of the national stroke population.

The suspected stroke population was defined by paramedic impression including stroke. Impression could be interpreted as a measure of certainty of diagnosis, with impression of stroke in isolation representing the highest level of certainty and impression including stroke in combination with multiple other diagnoses representing the lowest level of certainty. Impression is a subjective finding and how it is documented will vary between users. Paramedic impression of stroke is a logical inclusion criteria for this study, however the

subjective nature of the observation would make it a difficult characteristic to prospectively test or to include in a SM identification tool.

1.4.6.5 Physiological observations

Physiological observations were consistently recorded, apart from pain and temperature as mentioned earlier. Stroke and SM patients had very similar mean values for all physiological observations (table 1.4.8). There was a statistically significant difference ($p<0.05$) between all physiological observation mean values, with the exception of SaO2 and respiratory rate. The reported differences are statistically significant but the magnitude of the differences were too small to be considered clinically significant.

1.4.6.6 Past medical history

Twelve pertinent factors from patients' PMH relevant to the stroke or SM diagnosis were selected from the systematic review (see table 1.4.9) and extracted from the NEAS records. Hypertension, a recognised risk factor for stroke (Sacco, 1997), was the most frequently recorded finding and was significantly associated with stroke diagnosis. Previous stroke was the second most commonly recorded factor, but this was significantly associated with SM diagnosis. This may represent decompensation of existing symptoms or knowledge of the previous stroke unduly influencing the paramedic's suspected diagnosis. Diabetes was the third most commonly recorded PMH factor.

The three most commonly recorded items of PMH in patients in this study were also commonly recorded in national data (RCP, 2017a)(pg 36). The SSNAP report showed that hypertension (53%), stroke/TIA (26%) and diabetes (21%) were frequently recorded in stroke patients.

A statistically significant ($p<0.05$) difference between the frequency of recording in the stroke and SM populations was identified in 50% of the recorded factors (heart failure; hypertension; epilepsy; stroke; migraine; alcohol). Out of these six factors four were recorded on small (<4%) numbers of patients: alcohol, migraine, heart failure and epilepsy. In contrast a large percentage of the suspected stroke population had hypertension (30%) or previous stroke (27%) recorded. It is noteworthy that no statistically significant difference between stroke and SM patients was found in a number of common risk factors for cardiovascular disease such as alcohol misuse, smoking, diabetes and high cholesterol. These

factors were recorded on small numbers of patients and the presence of these risk factors may have been influential in the suspected diagnosis of stroke.

1.4.6.7 Signs and symptoms/general observations

Twenty-three observations or combinations of observations are reported in table 1.4.10. In 52% (n=12) there was a statistically significant difference in the rate of reporting between the stroke and SM populations.

The individual aspects of the FAST were the most commonly recorded items (Face 56%, arms 64%, speech 68%). The FAST itself was recorded for just over half (52%) of suspected stroke patients. The rate of recording of FAST appears low in this suspected stroke population and reasons for this are explored further in the next section. All of the elements of FAST were statistically associated with stroke diagnosis.

Leg weakness was frequently recorded (45% of suspected stroke patients) but this may have been due to interpretation of the recording of right or left sided weakness on the EPRF. In patients with limb weakness leg weakness was recorded in isolation in only 6% of cases and in combination with arm weakness in 94% of cases. Arm weakness was recorded without leg weakness in 33% of cases.

Confusion (29% of suspected stroke patients) and general weakness (23% of suspected stroke patients) were the next most frequently recorded observations. These are both non-specific observations that may be subject to reporter interpretation. It is not surprising that neither showed a statistically significant difference between the stroke and SM populations. Headache was the only other observation recorded in >10% of the populations. Headache was statistically different in the stroke and SM populations.

Apart from the factors associated with FAST, including leg weakness, the observations showing the greatest statistically significant difference between stroke and SM were seizures and unconscious (both $p<0.001$). Neither were recorded for large numbers of patients, but both were significantly associated with a final SM diagnosis.

1.4.6.8 Reported rate of SM

The rate of SM (41%) reported in this study is based on confident linkage of NEAS suspected stroke patients with hospital diagnoses. This rate is higher than the mean pre-hospital SM

rate reported in chapter 1.2 of 27% and higher than previous pre-hospital stroke research in the North East which reported 22-23% SM (Harbison *et al.*, 2003; Nor *et al.*, 2004). This study did include patients with reduced GCS which were excluded from the previous local studies. The SM rate in this study is exceeded by only one pre-hospital paper in the literature review which reported a SM rate of 43% (Gioia *et al.*, 2016). The paper by Gioia et al described a Canadian EMS service using CPSS, which is functionally identical to FAST. These authors also classified TIA with stroke so used similar definitions to those used in this chapter.

The SM rate is influenced by the tool used to initially identify stroke. The stroke identification tools used in pre-hospital care have a range of PPVs from 40-98 (Rudd *et al.*, 2016a). The range of PPV values implies a range of SM rates from 2-60%. The PPV reported for FAST was 62-89% which implies a SM rate of 11-38%. The SM rate reported in this chapter (41%) sits outside of this range. One reason for this could be the inclusion of FAST-ve patients in the sample described in this chapter. UK stroke guidelines specify the use of a recognised screening tool, such as FAST, but also leave clinicians an option to suspect stroke in patients with a negative screen (Intercollegiate Stroke Working Party, 2016) (pg 35) in recognition of the range of presentations that stroke can have and the limitations inherent in the tools.

Only 52% (n=900) of patients in this study were FAST+ve. If the FAST+ve patients are explored further, then 65% (n=582) had a stroke diagnosis which results in a 35% SM rate which is within the range of figures described by Rudd et al. When this was examined further a large number of patients had either facial weakness, arm weakness or slurred speech documented but not the FAST test. Other pre-hospital studies have identified similar issues with the way stroke is recorded in ambulance records (Williams *et al.*, 2017).

This led to the creation of a composite variable called ‘any FAST’ which included FAST+ve or any documentation of facial droop, arm weakness or slurred speech. Any FAST included 1,573 (90%) patients, 967 (61%) of whom had a stroke diagnosis which equates to a 39% SM rate. The inverse of ‘any FAST’ represents patients with no documented FAST test or FAST symptoms and these patients were classed as ‘true FAST-ve’. This study included 169 (10%) ‘true FAST-ve’ patients, 67 (40%) received a stroke diagnosis therefore 102 (60%) were SM. Williams et al (Williams *et al.*, 2017) found 34% of FAST negative suspected stroke patients admitted in an Australian pre-hospital study received a stroke diagnosis.

In addition to the influence of the screening tool, there are multiple reasons why the SM rate reported here is higher than would be expected from the literature. None of the pre-hospital papers in the literature review described a UK population so there may be national differences in SM rates. The literature described stroke, and SM, patients identified using a variety of stroke identification methods which will result in differing populations being identified. This study reports a larger sample than previous pre-hospital papers with one exception. Sequeira et al (Sequeira *et al.*, 2016) reported on SM in a sample of 3,376 patients who were screened as stroke, but this was in an American HEMS service so represents a specific population. The geographical area served by NHCT covers a mixed rural and urban area with an elderly demographic which may have influenced the SM rate. Personal communications with stroke researchers around the UK reveal that many stroke services assume that 50% of ambulance stroke admissions will be SM. Consequently, the figure of 41% SM may be closer to representing UK practice than the figure of 27% reported in the literature review.

The assumption that patients without a confirmed diagnosis from either SSNAP or NHCT HES were patients with SM conditions also influenced the reported SM rate. Performing a sensitivity analysis by excluding all patients with an assumed SM diagnoses (n=149) reduced the sample to 1,593 patients. The reduced sample included 1,033 patients with a stroke diagnosis and 560 patients with a SM diagnosis, this leads to a 35% SM rate.

Patients with an assumed SM diagnosis were significantly younger than patients with a confirmed SM diagnosis. Younger age is associated with increased likelihood of SM diagnosis which supports the assumption that the assumed SM patients were SM.

Explanations for the assumed SM population include patients unable to be linked with either SSNAP or HES due to a lack of identifying information recorded in the EPRF, as well as patients not admitted to NHCT who would not appear in HES or SSNAP. This would include patients who self-discharged from ED, patients who died in ED or during transfer and patients transferred to a different care provider e.g. specialist neurosurgery which is based at a different trust.

Understanding the reported SM rate is vital to the development of this overall project as this population will be used to inform the development of a pre-hospital SM identification tool.

Recognising the variation in documentation of FAST was addressed by the creation of the 'any FAST' and 'true FAST-ve' characteristics.

1.4.6.9 SM diagnoses

SM had a wide range of underlying diagnoses which was expected given the range of SM conditions identified in chapter 1.2. When SM diagnoses were examined using ICD-10 codes the large number of diagnoses (n=172) made it difficult to identify patterns. Converting the diagnoses into CCS codes allowed clinically similar conditions to be combined and patterns to be examined. The most common conditions, based on ICD-10 or CCS codes, are similar to the most common SM diagnoses identified in the literature review. The literature review combined pre-hospital SM diagnoses with other settings whereas the data are derived from a single pre-hospital setting.

Comparing the SM diagnoses summaries from NEAS/NHCT against the literature review using figures 1.4.5 and 1.2.3, the overall pattern of SM diagnoses were very similar. Nervous system was the most common level 1 CCS code followed by circulatory. Epilepsy and headache were the leading level 2 CCS groups within the level 1 nervous system category. There were some differences between the pattern of SM diagnoses in the NEAS/NHCT data and the data reported in the literature review. The literature review included 27% patients with an unknown/other diagnosis whereas the NEAS/NHCT data included 149 (21%) patients with an assumed SM diagnosis which may be the closest equivalent to the unknown/other diagnosis group. One other noticeable difference is that the NEAS/NHCT data includes 5% mental illness cases whereas these accounted for 10% of diagnoses in the literature review.

1.4.6.10 Key findings to inform SM identification tool development

The data described in this phase of the study will inform the development of the SM identification tool. The stroke and SM populations will be further analysed to identify predictive factors for SM diagnoses. The key findings from this study that will inform the development of the SM identification tool are:

- Younger age and female gender are associated with SM diagnosis.
- Mean physiological observations are very similar between stroke and SM patients.
- Previous stroke or the absence of hypertension may help discriminate between stroke and SM.

- Clinical information such as headache and seizure appear to differentiate stroke and SM patients.

1.4.6.11 Strengths and limitations

Strengths

- Pre-hospital data were confidently linked with hospital diagnoses.
- 1,742 patients is a large sample for pre-hospital stroke identification research.
- Data on a large number of characteristics that potentially differentiate stroke and SM patients were collected.
- Recognition that FAST can be recorded in different ways and requires interpretation.

Limitations

- Some NEAS suspected stroke admissions did not have a location.
- Some NEAS suspected stroke admissions to NHCT could not be linked.
- A small number of patients have an assumed diagnosis.
- Extraction of free-text data was subject to interpretation.
- These data were based on a single hospital catchment area.

1.4.7 Summary

The data presented in this chapter describes suspected stroke patients identified by NEAS linked with patient's final diagnoses from NHCT. This allowed the SM rate to be calculated (41%) and the cohort described in terms of stroke and SM patients. This chapter includes a large amount of data on the pre-hospital suspected stroke population. The data presented will be further analysed in the next chapter and used in the development of a SM identification tool.

Chapter 1.5 Development of a multivariable prediction tool to identify stroke mimic patients

1.5.1 Introduction

This chapter describes the primary research aim of this thesis i.e. development of a tool to identify SM patients amongst pre-hospital suspected stroke patients. The focus on SM in the pre-hospital setting distinguishes this tool from other stroke assessment and identification tools.

The data on suspected stroke patients transported to NHCT hospitals reported in chapter 1.4, supported by the findings of the systematic review (chapter 1.2) and the paramedic survey (chapter 1.3) were used to derive the content of a SM tool that was likely to be feasible and have clinical utility in the pre-hospital setting.

This chapter is structured following the TRIPOD guidelines for prediction model development (Collins *et al.*, 2015).

1.5.1.1 Background

This chapter describes the development of a clinical prediction tool. Clinical prediction tools inform clinical decisions by combining discrete observations to provide evidence based guidance as to the optimal decision, diagnosis or prognosis for the patient. Large datasets can be analysed, summarised and converted into tools which are then used to inform clinical practice. Clinical prediction tools were introduced in chapter 1.1.

It is important to consider the wider context of clinical prediction tools when selecting one for use in clinical practice, such as: the number available to choose from; concerns about usability; application to populations other than the original intended target; availability of the key information variables; the potential for bias in the development and human reliance on intuition and factors outside of the scope of the tool (Liao and Mark, 2003; Cook, 2008; Moons *et al.*, 2009a).

1.5.1.2 Desired outcome of SM identification tool

Diagnostic tools balance sensitivity and specificity according to the desired clinical application (Adams and Leveson, 2012). The intention of the SM tool was application after the initial suspicion of stroke had been established, using a sensitive assessment like FAST, but before a decision was made about the appropriate patient pathway. Due to the range of conditions that present as SM, and the desire for a very specific tool expressed by the surveyed paramedics in chapter 1.3, the decision was made to focus on high specificity and PPV and accept that this would result in low sensitivity.

As the tool had to be usable by a pre-hospital clinician with access to variable clinical information and the diagnostic equipment that is currently carried on ambulances, it had to be intuitive and quick to apply. Consideration of these factors led to the principle of 'simple and specific' which guided the development of the SM tool.

1.5.1.3 Target population

The pre-hospital suspected stroke population consists of two groups: the larger FAST+ve group, and a second group where the paramedic suspects that stroke is the most likely diagnosis because of other characteristics that are not included in FAST.

Applying the SM tool to all suspected strokes would increase the potential target population and would simplify application in clinical practice. Although the National Clinical Guideline (Intercollegiate Stroke Working Party, 2016) recommend the use of a suitable screening tool, such as FAST, to identify stroke, it also states that clinicians must use their own clinical judgement because some stroke symptoms are excluded by the commonly used tools. This approach also had the benefit of not linking the SM tool directly to an existing identification tool which might not be universally used and which may change in the future.

The second option considered was applying the tool only to FAST+ve suspected stroke patients. This had the benefit of targeting a more clearly defined suspected stroke population recognised by a commonly used, and validated, tool. Some pre-hospital services already exclude FAST-ve patients from their stroke pathways (UK pre-hospital stroke pathways are discussed further in chapter 4.0). This option would reduce the target population and exclude a group of patients that may include a high proportion of SM. Therefore, the target population for SM tool application was all suspected stroke patients.

This meant that the SM tool would need to be used sequentially after an initial screening test which identified the patient as a suspected stroke.

It is a recognised approach in health screening to use a simple initial test which is sensitive to the condition under examination in order to be inclusive, and then to refine the judgement with a second test which has greater precision i.e. lower rate of false positive cases (Doubilet and Cain, 1985; Macaskill *et al.*, 2002). This is known as sequential testing. This approach underpins the practice of population screening for conditions such as breast cancer followed by specific diagnostic testing to confirm or exclude the diagnosis (Public Health England, 2013).

In relation to pre-hospital stroke identification, the advantage of a sequential testing approach is that it would not change the initial provisional diagnosis of stroke, based upon FAST, another stroke identification tool or paramedic judgement, but would inform the subsequent response according to the results of the SM tool.

1.5.2 Chapter aims and objectives

The aim of this chapter is to describe the development of a SM identification tool.

The objectives are:

- To describe the decisions and criteria that were applied during the tool development process.
- To describe the multiple methods used to develop the tool.
- To describe the SM identification tool content.
- Describe the performance of the SM identification tool when retrospectively applied to a clinical ambulance dataset.

1.5.3 Methods

Clinical prediction tools are developed using one or more of the following five methods: univariate analysis; multivariate analysis; neural networks; nomograms; and classification and regression trees (Grobman and Stamilio, 2006).

The multivariable analysis method was chosen for this project, as the literature review revealed a range of common SM conditions which may be possible to identify using different

specific characteristics. Univariate analysis was used to inform the development of the multivariable model. Nomograms are graphical representations of clinical prediction tools, which can be challenging to interpret if several variables are involved and are not widely used in pre-hospital care. Neural networks require complex computational techniques and familiarity with machine learning so are beyond the scope of this work. Classification and regression tree analysis would produce a decision tree similar to many algorithms used in pre-hospital care but could oversimplify the outcomes where there are likely to be multiple predictive factors.

For a clinical prediction tool with a binary outcome, such as stroke or SM, multivariable logistic regression is a frequently adopted multivariate statistical analytical technique. This is due to its flexibility, ability to include categorical and continuous predictors, consideration of the weight of predictor variables and its overall reflection of the multivariable nature of clinical decision making.

Clinical prediction tools for SM were described in chapter 1.1. All of the SM tools, apart from one (Siddiqui *et al.*, 2016), were developed using multivariable analysis informed by initial univariate analysis. Multivariable models do have some weaknesses as they rely upon statistical assumptions about data distribution that need to be appropriately interpreted, furthermore the models produced may be influenced by interactions between predictor variables that can be difficult to identify (Grobman and Stamilio, 2006; Adams and Leveson, 2012).

1.5.3.1 Source of data

The SM tool was developed using retrospective pre-hospital clinical data collected from NEAS, linked with hospital diagnoses supplied by NHCT. The dataset included patients seen by NEAS paramedics during a three year period between 01/06/2013 and 31/05/2016. The creation of the dataset was described in chapter 1.4. The SM tool development was informed by the systematic review (chapter 1.2) and the survey of UK paramedics (chapter 1.3).

1.5.3.2 Participants

A development cohort was established using the 1,742 patients identified by NEAS as suspected stroke described in chapter 1.4.

The following inclusion and exclusion criteria were applied:

Inclusion

Suspected stroke patient conveyed by NEAS to NHCT with an impression including stroke between 01/06/2013 and 31/05/2016

Exclusion

GCS<8

Reduced consciousness level (GCS<8) was chosen as an exclusion criterion based upon standard pre-hospital practice. These patients are difficult to assess due to their lowered consciousness level and are normally rapidly transported to the nearest ED for assessment and stabilisation irrespective of their underlying condition. This decision was also informed by the original work on FAST (Harbison *et al.*, 2003) which specified that patients with GCS<8 were transported to ED as opposed to direct to a stroke unit.

1.5.3.3 Outcome

The outcome predicted by the SM identification tool is final discharge diagnosis of a non-stroke condition i.e. a binary state of stroke or SM. As discharge diagnoses were not available in the NEAS clinical records, it was necessary to obtain these from the receiving hospital trust i.e. NHCT.

1.5.3.4 Predictors

The predictors used in developing the SM identification tool were those variables described in chapter 1.4. The variables were selected based on the literature review (chapter 1.2), availability within the NEAS data and the clinical input of the supervisory team. Forty-nine variables (listed below), plus the patients' final diagnoses, were included in the development dataset.

Variables included in dataset:

Hospital discharge diagnosis; Impression; Age; Gender; BM; GCS; Heart Rate; Pain: Numeric; SaO2; Respiratory Rate; SBP; DBP; Temperature; Pulse regularity; PMH Angina; PMH Heart

Failure; PMH High Cholesterol; PMH Hypertension; PMH MI; PMH Diabetes; PMH Smoking; PMH Epilepsy; PMH Stroke; PMH TIA; PMH Migraine; PMH Alcohol misuse; Dizziness; General weakness; Nausea or vomiting; Syncope; Chest pain; Abnormal gait; Arm weakness; Confusion; Facial droop or weakness; Floppy; Headache; Leg weakness; Neck Stiffness; Seizures; Speech symptoms; Tremors; Unconscious; FAST+ve; True FAST-ve; Alcohol/Drug use reported; AF; Eye issues; Visual disturbances; Altered Sensation

1.5.3.5 Sample size

No formal sample size calculation was performed for the development dataset. All available data were used. Based on the rule of >10 cases per predictor variable being necessary for a regression model (Vittinghoff and McCulloch, 2007; Austin and Steyerberg, 2015) the sample needed to include >980 patients (>490 stroke patients and >490 SM patients) to fulfil this criterion.

1.5.3.6 Missing data

Patients with missing data were included within the dataset. Missing data were assumed to be randomly distributed apart from SBP and DBP. SBP and DBP are observed, collected and documented as a pair and so they were considered to be linked. The linkage between SBP and DBP is relevant when considering multicollinearity which is discussed later in this chapter. Missing data were identified using the code '999' for analysis within SPSS. There was no imputation or adjustment in variable weighting used in the analysis.

1.5.3.7 Statistical analysis methods

All data were collected in Microsoft Excel and imported into SPSS 23 or SigmaPlot 12.5 for analysis. Statistical advice was taken on the regression analysis and the use of SPSS from the Newcastle University statistical support team.

1.5.3.8 Univariate analysis

Univariate analysis was performed on all 49 candidate variables. This was done to identify suitable variables, defined as those with $p<0.2$, for inclusion in the multivariable logistic analysis.

Continuous variables, primarily physiological measurements, were tested for differences in the outcome using the independent samples t-test. Categorical variables, including presence

of relevant items of medical history or presenting signs and symptoms, were tested using the chi squared test.

1.5.3.9 Multivariable analysis

Binary logistic regression (BLR) was the multivariable method chosen to analyse the data. BLR is a form of regression analysis where the variable of interest (dependent variable) is binary in nature and there are multiple explanatory (predictor) variables. BLR was a suitable method as the outcome was binary, stroke or SM, and there were a large number (n=49) of candidate variables. BLR allowed identification of statistically significant predictor variables and the magnitude of their association with the outcome.

BLR was an appropriate technique because:

- Few distributional assumptions are made.
- The dependent variable is dichotomous (stroke or SM).
- Due to the size of the sample (>30) the central limit theorem allows a normal distribution to be assumed (Field, 2013) (p54).
- Multicollinearity amongst predictor variables can be identified.
- Combinations of continuous and discrete variables can be used.
- Extra data can be easily added once the initial dataset is established.

BLR has been used in a number of studies with similar aims and datasets (Chang *et al.*, 2012; Ali *et al.*, 2014; Goyal *et al.*, 2016b) so there was a precedent for using BLR in this thesis.

1.5.3.10 Receiver operating characteristic curves

Receiver Operating Characteristic (ROC) curves (introduced in chapter 1.1) were generated for the continuous variables using Sigmaplot 12.5 software.

1.5.4 Results

The development dataset is described using characteristics selected as clinically plausible predictors where the relevant information would be available to paramedics. Associations between the characteristics are reported in terms of collinearity and correlation. Additional information on the recording of FAST and paramedic impression are also reported.

1.5.4.1 Univariate analysis of the development dataset

Applying the inclusion and exclusion criteria to the dataset described in chapter 1.4 resulted in 1,650 suspected stroke patients in the development dataset. The dataset is described in table 1.5.1 along with the results of the univariate analysis to identify initial associations with stroke/SM diagnosis.

Table 1.5.1 Characteristics of SM identification tool development cohort

	Patients with observation documented (% total)	**Stroke**	**SM**	**p value**
Patients		989 (60%)	661 (40%)	
Mean age (SD)	100%	77 (12)	73 (15)	<0.001
Gender (% male)	100%	50%	41%	<0.001
Physiological observation		**Stroke (mean, SD)**	**SM (mean, SD)**	
BM (mmol/l)	96%	7.6 (2.7)	7.2 (2.3)	0.002
GCS	100%	14 (2)	14 (2)	0.510
Heart rate	100%	82 (19)	85 (20)	0.004
Irregular pulse	97%	25%	18%	0.003
Pain (0-10)	65%	0.3 (1.2)	0.5 (1.6)	0.020
SaO2	99%	96 (3)	96 (3)	0.299
Respiratory rate	100%	17 (3)	17 (3)	0.171
SBP (mmHg)	99%	160 (28)	153 (30)	<0.001
DBP (mmHg)	99%	89 (17)	87 (19)	0.024
Temperature (Celsius)	87%	36.4 (0.7)	36.6 (1.0)	0.001
Past Medical History		**% stroke patients**	**% SM patients**	
Alcohol misuse	1%	1%	2%	0.013
Angina	8%	8%	9%	0.812
Diabetes	16%	17%	15%	0.268
Epilepsy	3%	2%	6%	<0.001

Table 1.5.1 Characteristics of SM identification tool development cohort cont.				
	Patients with observation documented (% total)	**Stroke**	**SM**	**p value**
Heart failure	2%	3%	1%	0.007
High cholesterol	14%	14%	13%	0.491
Hypertension	30%	33%	25%	<0.001
MI	9%	9%	7%	0.179
Migraine	2%	<1%	3%	0.004
Smoking	2%	2%	2%	0.682
Stroke	27%	24%	31%	0.001
TIA	16%	16%	16%	0.983
Signs and symptoms		**% stroke patients**	**% SM patients**	
Abnormal gait	10%	11%	8%	0.072
AF	12%	15%	8%	<0.001
Alcohol/Drug use reported	2%	2%	3%	0.460
Altered Sensation	8%	9%	7%	0.309
Arm weakness	63%	73%	48%	<0.001
Chest pain	1%	1%	2%	0.066
Confusion	30%	28%	32%	0.149
Dizziness	8%	8%	8%	0.900
Eye issues	6%	7%	4%	0.004
Facial droop or weakness	54%	60%	45%	<0.001
FAST+ve	53%	58%	47%	<0.001
Floppy	6%	7%	5%	0.109
General weakness	25%	23%	28%	0.028
Headache	21%	19%	25%	0.006
Leg weakness	46%	55%	31%	<0.001

Table 1.5.1 Characteristics of SM identification tool development cohort cont.				
	Patients with observation documented (% total)	**Stroke**	**SM**	**p value**
Nausea or vomiting	11%	10%	13%	0.110
Neck Stiffness	1%	1%	2%	0.338
Seizures	4%	2%	7%	<0.001
Speech symptoms	64%	70%	56%	<0.001
Syncope	1%	1%	1%	0.113
Tremor	3%	2%	4%	0.001
True FAST-ve	8%	6%	11%	<0.001
Unconscious	5%	3%	8%	<0.001
Visual disturbances	8%	7%	8%	0.633

1.5.4.2 Distribution of physiological variables

The physiological variables were reported as means but this may have hidden differences in stroke and SM patient distributions. In order to address this and explore if subgroups within these observations were relevant to differentiating stroke and SM, frequency distribution plots were constructed. The frequency distribution plots can be found in appendix G.

The frequency distribution plots of the physiological variables revealed broadly similar distribution patterns between stroke and SM patients although there were some differences at the extremes of some variables such as age.

1.5.4.3 Multicollinearity

Multicollinearity describes the presence of correlation between predictor variables that unduly influences the output of a regression analysis.

All variables were tested for multicollinearity by examining the Variance Inflation Factor (VIF) and tolerance statistics. Individual VIF>10 or average VIF<1 are causes for concern that multicollinearity may be present (Field, 2013) (p 325). The mean VIF was 1.275. The only

variables with VIF>2 were SBP (2.458) and DBP (2.600). Tolerance <0.2 indicates there may be a problem with multicollinearity. The mean tolerance was 0.812. The only variables with tolerance<0.5 were SBP (0.407) and DBP (0.385).

The physiological observations were predominantly reported as continuous variables. Due to the interdependent relationships between these variables, they were thought to be more at risk of correlation than the other measurements. The physiological continuous variables were examined for correlation using a correlation matrix (table 1.5.2).

Correlations

		Age	BM	Glasgow Coma Scale	Heart Rate (BPM)	Pain: Numeric	Peripheral Oxygen Saturation (%)	Respiratory Rate (BPM)	Systolic Blood Pressure	Diastolic Blood Pressure	Temperature
Age	Pearson Correlation	1	.000	-.160**	-.087**	-.165**	-.187**	.016	.051*	-.142**	-.021
	Sig. (2-tailed)		.992	.000	.000	.000	.000	.516	.041	.000	.419
	N	1643	1579	1643	1640	1062	1632	1641	1628	1625	1428
BM	Pearson Correlation	.000	1	-.041	.089**	.016	-.071**	.053*	.031	.008	.015
	Sig. (2-tailed)	.992		.105	.000	.620	.005	.035	.220	.741	.585
	N	1579	1585	1585	1583	1023	1576	1584	1576	1573	1387
Glasgow Coma Scale	Pearson Correlation	-.160**	-.041	1	-.093**	.098**	.206**	-.102**	.056*	-.010	.089**
	Sig. (2-tailed)	.000	.105		.000	.001	.000	.000	.023	.699	.001
	N	1643	1585	1650	1646	1067	1638	1647	1634	1631	1434
Heart Rate (BPM)	Pearson Correlation	-.087**	.089**	-.093**	1	-.015	-.162**	.196**	.026	.200**	.194**
	Sig. (2-tailed)	.000	.000	.000		.628	.000	.000	.294	.000	.000
	N	1640	1583	1646	1646	1066	1636	1644	1632	1629	1432
Pain: Numeric	Pearson Correlation	-.165**	.016	.098**	-.015	1	.046	.023	.035	.056	-.030
	Sig. (2-tailed)	.000	.620	.001	.628		.137	.459	.249	.067	.360
	N	1062	1023	1067	1066	1067	1058	1066	1059	1057	942
Peripheral Oxygen Saturation (%)	Pearson Correlation	-.187**	-.071**	.206**	-.162**	.046	1	-.213**	.127**	.080**	-.034
	Sig. (2-tailed)	.000	.005	.000	.000	.137		.000	.000	.001	.198
	N	1632	1576	1638	1636	1058	1638	1636	1625	1622	1425
Respiratory Rate (BPM)	Pearson Correlation	.016	.053*	-.102**	.196**	.023	-.213**	1	.005	.027	.057*
	Sig. (2-tailed)	.516	.035	.000	.000	.459	.000		.826	.277	.032
	N	1641	1584	1647	1644	1066	1636	1647	1632	1629	1432
Systolic Blood Pressure	Pearson Correlation	.051*	.031	.056*	.026	.035	.127**	.005	1	.698**	.033
	Sig. (2-tailed)	.041	.220	.023	.294	.249	.000	.826		.000	.219
	N	1628	1576	1634	1632	1059	1625	1632	1634	1631	1425
Diastolic Blood Pressure	Pearson Correlation	-.142**	.008	-.010	.200**	.056	.080**	.027	.698**	1	-.032
	Sig. (2-tailed)	.000	.741	.699	.000	.067	.001	.277	.000		.234
	N	1625	1573	1631	1629	1057	1622	1629	1631	1631	1423
Temperature	Pearson Correlation	-.021	.015	.089**	.194**	-.030	-.034	.057*	.033	-.032	1
	Sig. (2-tailed)	.419	.585	.001	.000	.360	.198	.032	.219	.234	
	N	1428	1387	1434	1432	942	1425	1432	1425	1423	1434

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 1.5.2 Correlation matrix of continuous physiological variables

A number of statistically significant (p<0.05) correlations were identified. When the relative strengths of the correlations were examined (represented by the Pearson correlation) then the only variables which were more than 'weakly' correlated (Pearson correlation coefficients 0.20-0.39) were SBP and DBP which displayed a 'strong' (0.60-0.79) correlation (Mukaka, 2012).

Due to the link between SBP and DBP in both the multicollinearity testing and the correlation matrix, DBP was removed from the tool development, as it is less predictive of an abnormal physiological state than the broader range of SBP.

1.5.4.4 Inclusion of the FAST test

FAST was considered as a predictor variable for the SM tool. Reliance on the FAST+ve variable was problematic due to the issues identified in chapter 1.4. Therefore the 'Any FAST' and 'True FAST-ve' variables were created. 'Any FAST' includes FAST+ve or any combination of FAST elements. 'True FAST-ve' is where 'AnyFAST'=0. The dataset is described by 'Any FAST' and 'True FAST-ve' in table 1.5.3.

Table 1.5.3 Cohort described by composite FAST variables

	Patients with observation documented (% total)	Stroke	SM	p value
Any FAST	92%	94%	89%	<0.001
True FAST-ve	8%	6%	11%	<0.001

1.5.4.5 Impression

Ambulance clinician impression was also considered as a variable that could be included in the SM identification tool. Data on impression were reported in chapter 1.4, table 1.4.7 from chapter 1.4 is repeated below, and showed a trend where impression 'stroke' > impression 'stroke and TIA' > impression 'stroke plus others' in terms of accuracy of stroke diagnosis.

Table 1.4.7 Paramedic impression and final diagnoses

Impression	Total patients	Stroke	SM
Stroke only	1353	881 (65%)	472 (35%)
Stroke and TIA	132	74 (56%)	58 (44%)
Stroke plus others	257	78 (30%)	179 (70%)

However, impression was not included as a variable in the SM identification tool development due to its subjective nature.

1.5.5 Model development stage 1 – the regression model

The first attempt at developing a SM tool used BLR to generate a model which would detect SM with the best balance of sensitivity and specificity. This represented an inclusive attempt to detect the maximum number of SM based on all the available data.

The following variables (n=34) were selected for inclusion in the BLR based upon results of univariate analyses at $p<0.2$ (Labopin and Iacobelli, 2003):

Age; gender; BM; heart rate; irregular pulse; pain; respiratory rate; SBP; temperature; PMH alcohol; PMH epilepsy; PMH heart failure; PMH hypertension; PMH MI; PMH migraine; PMH stroke; abnormal gait; AF; arm weakness; chest pain; confusion; eye issues; facial droop; true FAST-; floppy; general weakness; headache; leg weakness; nausea or vomiting; seizures; speech symptoms; syncope; tremors; unconscious.

Although there were a large number of potential predictor variables at this stage, based on the rule of thumb that for each explanatory variable >10 patients are needed, the sample was above the minimum number acceptable.

Using the 'Forward likelihood ratio' method in SPSS (which was chosen due to the large number of variables and the exploratory nature of the first analysis) all 34 variables were entered into a BLR. The model included 875 (53.0%) of cases. The model produced included 12 predictor variables (shown below in table 1.5.4), was statistically significant (X^2 (12) = 175.891, $p<0.001$) and explained 24.7% of the variance in stroke/SM diagnosis (Nagelkerke R^2). The model had a sensitivity of 51.2%, specificity 84.9% and a PPV of 68.1% for SM.

The regression model excluded a large number of cases due to missing data. Pain (recorded in 65% of all patients) and temperature (recorded in 87% of all patients) accounted for the majority of the missing data. A second BLR was run with these two variables removed.

Table 1.5.4 Variables in the regression modelv1

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 12[l]	Age	-.027	.006	19.850	1	.000	.974
	Gender(1)	-.523	.157	11.127	1	.001	.593
	BM	-.112	.035	9.916	1	.002	.894
	Systolic Blood Pressure	-.010	.003	13.567	1	.000	.990
	PMH Epilepsy(1)	-1.408	.499	7.950	1	.005	.245
	PMH Stroke(1)	-.372	.175	4.513	1	.034	.689
	Arm weakness(1)	.857	.192	19.835	1	.000	2.356
	Leg weakness(1)	.546	.191	8.164	1	.004	1.726
	Speech symptoms(1)	.671	.165	16.490	1	.000	1.956
	Tremors(1)	-1.246	.430	8.393	1	.004	.288
	Unconsciousness(1)	-.973	.394	6.085	1	.014	.378
	FT Eye issues(1)	1.366	.643	4.507	1	.034	3.920
	Constant	5.780	1.198	23.290	1	.000	323.722

Using the 'Forward likelihood ratio' method in SPSS 32 variables were entered into a BLR. The model included 1,524 (92.4%) of cases. The model produced included 19 predictor variables (shown below in table 1.5.5), was statistically significant, (X^2 (19) = 338.483, $p<0.001$) and explained 27.0% of the variance in stroke/SM diagnosis (Nagelkerke R^2). The model had a sensitivity of 53.2%, specificity 81.6% and a PPV of 65.2% for SM.

Table 1.5.5 Variables in the regression modelv2

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 19[s]	Age	-.021	.005	19.920	1	.000	.979
	Gender(1)	-.519	.121	18.486	1	.000	.595
	BM	-.058	.024	5.753	1	.016	.943
	Systolic Blood Pressure	-.011	.002	25.857	1	.000	.989
	PMH CHF(1)	1.020	.448	5.171	1	.023	2.772
	PMH Hypertension(1)	.283	.133	4.546	1	.033	1.327
	PMH Epilepsy(1)	-1.017	.345	8.716	1	.003	.362
	PMH Stroke(1)	-.451	.132	11.753	1	.001	.637
	Arm weakness(1)	.839	.153	30.054	1	.000	2.314
	Confusion(1)	-.348	.131	7.098	1	.008	.706
	Facial droop or weakness(1)	.366	.127	8.331	1	.004	1.442
	Headache(1)	-.401	.147	7.401	1	.007	.670
	Leg weakness(1)	.666	.145	21.005	1	.000	1.947
	Seizures(1)	-1.079	.350	9.498	1	.002	.340
	Speech symptoms(1)	.597	.137	18.945	1	.000	1.816
	Tremors(1)	-1.139	.372	9.363	1	.002	.320
	Unconsciousness(1)	-.687	.285	5.825	1	.016	.503
	AF(1)	.394	.192	4.236	1	.040	1.483
	TrueFASTneg(1)	.653	.261	6.284	1	.012	1.922
	Constant	4.935	1.016	23.600	1	.000	139.076

The results of these BLR models were informative, however the aim was to produce a tool with a higher specificity and PPV than either of these models achieved, and the large number of factors with variable weightings would be a barrier to clinical application. The models generated by the BLR sought the best balance of sensitivity and specificity, but these did not attain the high specificity which was necessary based on the national paramedic survey reported in chapter 1.3. Based on the analyses it became obvious that a generic SM tool would not meet the aims of this project as it was neither simple nor specific. This led to reconsidering the adopted approach and a move away from a comprehensive predictive approach focussed on high sensitivity and high specificity. What was needed was a tool

focused on specificity and PPV with the acceptance that this could only be achieved at the expense of sensitivity and with a different approach.

1.5.6 Model development stage 2 – the focussed model

Developing a SM identification tool focused on high specificity and PPV was the preferred option for a number of reasons:

- Due to the wide range of SM aetiologies and variable associations with clinical characteristics developing a generic tool seemed impractical.
- The intention of the SM tool was that it would be applied after the initial suspicion of stroke was established so sensitivity was not the most important measure of performance.
- The relative consequences of failure to recognise stroke were considered to be greater than failure to recognise SM due to the time-critical nature of treatment.
- This was reinforced by the survey reported in chapter 1.3 which indicated that paramedics wanted a SM tool to be very highly specific.

Odds ratios (OR) were used to inform the development of a more focussed tool.

"*An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure*." (Szumilas, 2010).

Odds ratios (OR) were calculated to quantify the strength of each predictor's association with SM diagnosis. These were then used to select the predictor variables with the strongest association with SM diagnosis for inclusion in a focussed SM tool.

The continuous variables (age; BM; GCS; heart rate; pain; SaO2; respiratory rate; SBP; temperature) were converted into binary predictors as the wide range of possible values for each created complex weighting coefficients which reduced the clinical utility. The optimum cut-off points were calculated using AUC generated by ROC analysis as shown in table 1.5.6.

Table 1.5.6 ROC analysis of continuous physiological variables					
Variable	**Cut-off**	**% SM based on cut-off**	**P value**	**Sensitivity**	**Specificity**
Age	<52	71	<0.0001	0.10	0.97
BM	<4.6	68	0.01	0.04	0.99
GCS	<8	0	0.17	0.00	1
Heart rate	>179	0	0.003	0.00	1
Pain	>7	71	0.16	0.01	1
SaO2	>99.8	42	0.91	0.00	1
Respiratory rate	>31	67	0.10	0.01	1
SBP	<95	80	<0.0001	0.02	1
Temperature	>37.7	70	<0.0001	0.08	0.98

The cut-off values calculated in the ROC analysis were used to dichotomise the continuous variables and calculate OR. OR were not calculated for GCS, pain, SaO2 or respiratory rate based on statistical non-significance ($p>0.05$) in the ROC analysis. Heart rate was also excluded as there was only one patient with HR>179. The OR for all variables are shown in table 1.5.7. As the outcome of interest was SM diagnosis an OR>1 was associated with SM diagnosis and OR<1 was associated with stroke diagnosis.

Table 1.5.7 Odds ratios of predictor variables for SM diagnosis			
	Odds ratio	**Lower 95% CI**	**Upper 95% CI**
Age<52	4.0	2.5	6.3
Gender (female)	1.5	1.2	1.8
Physiological observation			
BM<4.6mmol/l	3.3	1.6	6.6
Irregular pulse	0.7	0.5	0.9
SBP<95mmHg	6.7	1.9	23.6
Temperature>37.7^{o}C	3.8	2.1	6.7

Table 1.5.7 Odds ratios of predictor variables for SM diagnosis cont.			
	Odds ratio	**Lower 95% CI**	**Upper 95% CI**
Past Medical History			
Alcohol misuse	2.8	1.2	6.8
Angina	1.0	0.7	1.5
Diabetes	0.9	0.7	1.1
Epilepsy	4.0	2.2	7.2
Heart failure	0.4	0.2	0.8
High cholesterol	0.9	0.7	1.2
Hypertension	0.7	0.5	0.8
MI	0.8	0.5	1.1
Migraine	3.2	1.4	7.6
Smoking	0.9	0.4	1.7
Stroke	1.5	1.2	1.8
TIA	1.0	0.8	1.3
Signs and symptoms			
Abnormal gait	0.7	0.5	1.0
AF	0.5	0.4	0.7
Alcohol/Drug use reported	1.3	0.7	2.5
Altered Sensation	0.8	0.6	1.2
Arm weakness	0.3	0.3	0.4
Chest pain	2.5	0.9	7.0
Confusion	1.2	0.9	1.5
Dizziness	1.0	0.7	1.4
Eye issues	0.5	0.3	0.8
Facial droop or weakness	0.6	0.5	0.7
FAST+ve	0.7	0.5	0.8
Floppy	0.7	0.5	1.1
General weakness	1.3	1.0	1.6
Headache	1.4	1.1	1.8
Leg weakness	0.6	0.3	0.4

Table 1.5.7 Odds ratios of predictor variables for SM diagnosis cont.			
	Odds ratio	**Lower 95% CI**	**Upper 95% CI**
Nausea or vomiting	1.3	0.9	1.7
Neck Stiffness	1.5	0.6	3.5
Seizures	4.3	2.4	7.8
Speech symptoms	0.6	0.4	0.7
Syncope	2.2	0.8	6.4
Tremor	2.6	1.4	4.8
True FAST-ve	2.2	1.5	3.1
Unconscious	3.3	2.0	5.3
Visual disturbances	1.1	0.8	1.6

Using the information from the initial regression models, the frequency distribution graphs and the OR, variables such as younger age, gender, PMH epilepsy, seizures and hypotension (low blood pressure) were identified that were consistently associated with SM diagnosis which was supported by the literature review (chapter 1.2).

This information was used to identify smaller groups of patients who were more likely to be SM. The smaller groups were selected based on clinical presentations associated with SM diagnoses such as seizures or sepsis and the presence of predictor variables. These groups were further explored using univariate and BLR analyses to identify predictive variables within these reduced populations. Through this process a small number of predictive variables started to emerge. Younger age, history of epilepsy and high temperature were all strongly associated with SM diagnosis in the literature and in the analyses.

Using these target populations with common SM presentations and the emerging predictive variables, a decision tree was constructed to identify each population by focussing on its unique predictive variables. Figure 1.5.1 illustrates the combinations of populations and predictor variables that were considered, and how a model focussed on these target populations was envisaged. Different populations were identified and predictive variables in these smaller populations were sought and are documented at the end of each pathway.

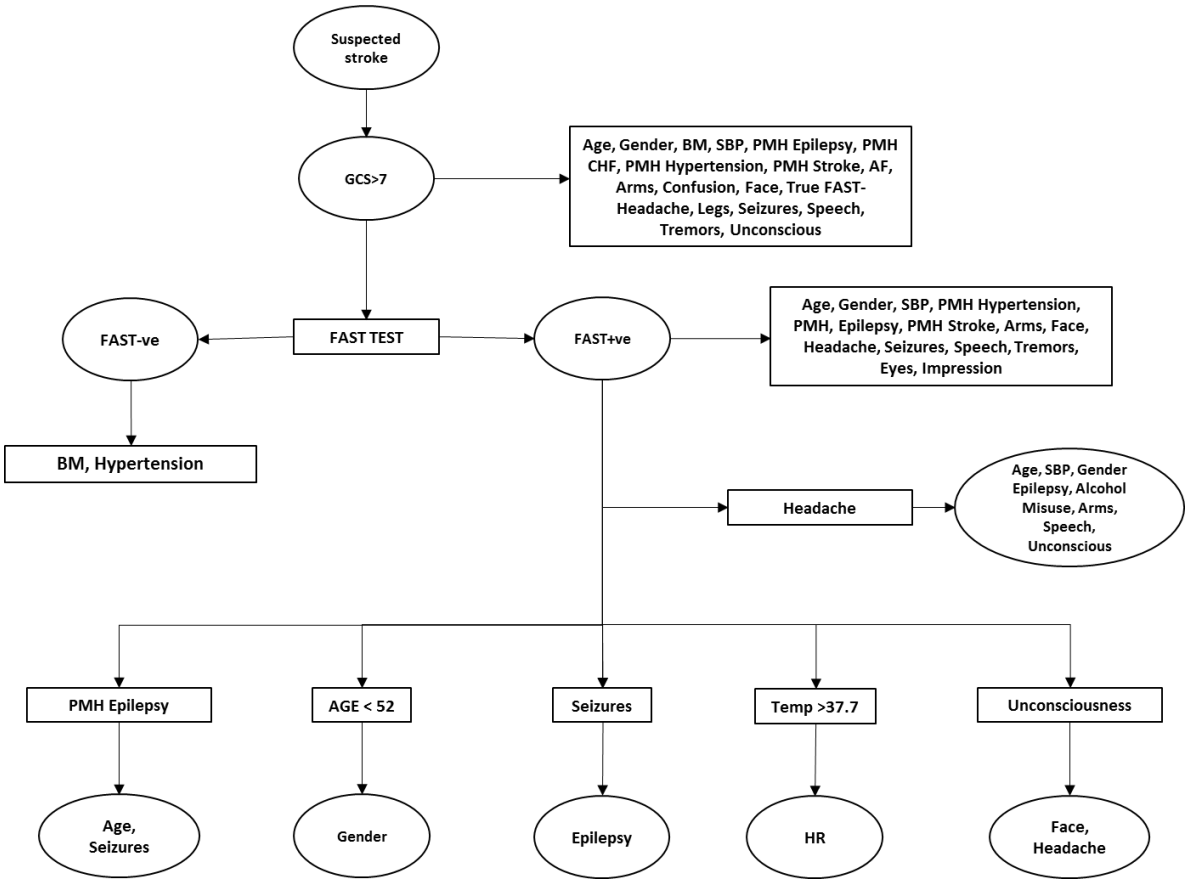


Figure 1.5.1 Model of decision tree SM identification tool

The aim of this thesis was to develop a simple tool whereas what emerged was a complicated and unwieldy tool based on differing combinations of individual variables which were predictive in small, distinct sub-populations.

1.5.7 Model development stage 3 – the combined model

The final stage in the tool development process involved organising, weighting and exploring the variables according to their strength of association and known clinical value. Rather than treating all the variables as independent predictors, clinically meaningful combinations were sought. Variables were regarded as clinically meaningful if they pointed towards a common SM diagnosis, or were characteristics strongly associated with SM diagnosis, which had been identified in the literature review (chapter 1.2). Individual variables were ranked according to OR and the strongest individual predictors (OR>3 or <0.3) were considered for inclusion either individually, or in combination with other variables.

1.5.7.1 Individual predictor variables

Age, SBP and BM were included in the BLR models and had good individual OR for predicting SM, but for inclusion in the SM tool it was necessary to explore their threshold values to convert them into binary predictors.

The optimum cut-off for age that was indicated by the ROC analysis was <52 years. This age cut-off identified 28 stroke patients and 69 SM patients, which was not acceptable due to the high number of stroke patients identified. Individual age values were considered, as shown in table 1.5.8, to identify a more suitable cut-off point for inclusion in the SM tool. Age<40 years gave an acceptable balance of stroke and SM patients, was lower than the age (50 years) used in other SM tools (Ali *et al.*, 2014; Goyal *et al.*, 2016b; Siddiqui *et al.*, 2016), and reflected specialist views about the age below which a vascular cause for stroke symptoms was less likely (Nacu *et al.*, 2016), so was included in the SM identification tool.

Table 1.5.8 Individual age values with number of stroke and SM patients identified by each value

Age (years)	Stroke	Stroke running total	SM	SM running total	Grand total	% SM
22		0	2	2	2	100%
24		0	2	4	4	100%
25		0	2	6	6	100%
30	1	1	1	7	8	88%
32		1	1	8	9	89%
33		1	3	11	12	92%
34		1	2	13	14	93%
35	1	2	1	14	16	88%
36		2	1	15	17	88%
37	2	4	3	18	22	82%
38		4	1	19	23	83%
39	1	5	4	23	28	82%
40	2	7	6	29	36	81%

Table 1.5.8 Individual age values with number of stroke and SM patients identified by each value cont.						
Age (years)	**Stroke**	**Stroke running total**	**SM**	**SM running total**	**Grand total**	**% SM**
41	2	9	1	30	39	77%
42	2	11	1	31	42	74%
43	1	12	3	34	46	74%
44	3	15	1	35	50	70%
45	1	16	4	39	55	71%
46	1	17	3	42	59	71%
47	2	19	2	44	63	70%
48	2	21	4	48	69	70%
49	4	25	10	58	83	70%
50	3	28	6	64	92	70%
51		28	5	69	97	71%

SBP was included in both BLR models and when split according to the ROC analysis at SBP<95mmHg was the strongest individual predictor based on OR (6.7). SBP<95mmHg identified 3 stroke patients and 12 SM patients. Increasing or decreasing the SBP value was considered to see what impact this would have on the predictive power of the variable, the results of this are shown in table 1.5.9. As there was no improvement in discrimination between states, SBP<95mmHg was retained and included in the SM identification tool.

Table 1.5.9 SBP values considered for inclusion in SM tool		
SBP (mmHg)	**Stroke**	**SM**
100	8	16
95	3	12
90	3	8
85	2	5

BM was considered for inclusion as a predictor variable as it was included in both BLR models and when split using ROC analysis at BM<4.6mmol/l it was strongly predictive (OR 3.3) of SM diagnosis. BM<4.6mmol/l identified 12 stroke patients and 25 SM patients. Lowering the BM value to 4.0mmol/l identified 4 stroke patients and 7 SM patients. Lowering it again to 3.5mmol/l, as per the NEAS guidelines for suspected stroke assessment, identified 1 stroke patient and 3 SM patients.

Based on the high proportion of stroke patients identified, unless BM<3.5mmol/l was used, and the fact that hypoglycaemia was already included as an exclusion criteria in the NEAS pre-hospital stroke pathway, the decision was made not to include BM in the SM identification tool at this point. As BM was already part of the stroke identification process, patients with stroke like symptoms due to hypoglycaemia may not have been included in the data as they were treated by the paramedics and documented as diabetic emergencies rather than stroke. This would mean that there would be very little data on this group within our population so showing predictive utility would be challenging.

1.5.7.2 Combined predictor variables

In addition to the individual variables, combinations of variables predictive of SM diagnoses were considered for inclusion. Seizures were identified by the literature review (chapter 1.2) as a common SM. PMH epilepsy and seizures were individually strong predictors of SM diagnoses (OR 4.0 and 4.3). Clinically it made sense to combine these two predictor variables to identify patients who had a PMH of epilepsy and a seizure to increase confidence in this possible SM diagnosis. This combined variable identified 1 stroke patient and 15 SM patients and had an OR of 22.9.

Migraine was also recognised as a common SM diagnosis. The variables clinically indicative of migraine in this dataset were PMH migraine and headache. PMH migraine had a strongly predictive OR (3.2) but headache was less predictive (OR 1.4). The combination of PMH migraine and headache identified 4 stroke patients and 12 SM patients with an OR of 4.6.

Raised temperature (>37.7^{o}C) had a high OR (3.8), but in isolation did not point towards a specific SM diagnosis, plus it identified a large number of stroke patients (n=17) compared to the number of SM patients (n=40). Considering sepsis as a common SM, and the sepsis indicators within the Systemic Inflammatory Response Syndrome (SIRS) criteria developed

by the Surviving Sepsis Campaign (Bone *et al.*, 1992), other predictor variables which could link temperature to sepsis diagnosis were identified. Tachycardia (raised heart rate) of >90 was another SIRS indicator of sepsis which was considered in combination with raised temperature. When heart rate>90 was combined with temperature>37.7^{o}C the combination identified 6 stroke patients and 28 SM patients. Due to the high number of stroke patients, refinements to this variable were considered.

The National Early Warning Score (NEWS) (RCP, 2012) is a physiological scoring system which includes temperature and heart rate which was in common use in hospital and growing use in pre-hospital care. The temperature predictor variable was raised to >38.0^{o}C to bring it into line with NEWS. Heart rate>90 was an existing NEWS variable. This combination of temperature>38.0^{o}C and heart rate>90 identified 2 stroke patients and 18 SM patients and had an OR of 14.3.

The dataset was examined for other variables that in combination had better predictive power if added to the SM tool. As unconscious was a strong predictor based on OR (3.3) and was included in both BLR models, other variables were reviewed that could in combination increase its predictive power. Combining unconscious with headache, another predictor of SM diagnosis, plus absence of facial weakness, the presence of which is a strong predictor of stroke diagnosis, generated a strong predictive combination. Unconscious plus headache without facial weakness identified 0 stroke patients and 9 SM patients.

1.5.7.3 Combining predictor variables into a tool

With a selection of individual and combined clinically meaningful predictor variables, targeting common SM conditions or characteristics, a scoring system was devised based on the aim of developing a simple and specific tool for pre-hospital use. Variables that were predictive of SM diagnoses were allocated a single point so that they could be combined to form a pragmatic scoring system. Variables were not weighted at this stage. This led to an iterative process where predictive factors were incrementally combined to create an initial SM tool.

Step 1. Age<40 years = 1 point (n=28)

- Patients scoring 1 point = 28 comprising 23 (82%) SM and 5 (18%) strokes

Step 2. Include seizures AND PMH epilepsy = 1 point (n=16)

- Patients scoring 1 point = 40 comprising 34 (85%) SM and 6 (15%) strokes
- Patients scoring 2 points = 2 comprising 2 (100%) SM
- Patients scoring 1 or 2 points = 42 comprising 36 (86%) SM and 6 (14%) stroke

Step 3. Include headache AND PMH migraine = 1 point (n=16)

- Patients scoring 1 point = 50 comprising 42 (84%) SM and 8 (16%) strokes
- Patients scoring 2 points = 5 comprising 4 (80%) SM and 1 (20%) stroke
- Patients scoring 1 or 2 points = 55 comprising 46 (84%) SM and 9 (16%) stroke

Step 4. Include Unconscious AND headache WITHOUT facial weakness = 1 point (n=9)

- Patients scoring 1 point = 53 comprising 45 (85%) SM and 8 (15%) strokes
- Patients scoring 2 points = 8 comprising 7 (88%) SM and 1 (12%) stroke
- Patients scoring 1 or 2 points = 61 comprising 52 (85%) SM and 9 (15%) stroke

Step 5. Include SBP<95mmHg = 1 point (n=15)

- Patients scoring 1 point = 68 comprising 57 (84%) SM and 11 (16%) strokes
- Patients scoring 2 points = 8 comprising 7 (88%) SM and 1 (12%) stroke
- Patients scoring 1 or 2 points = 76 comprising 64 (84%) SM and 12 (16%) stroke

Step 6. Include temperature>38.0^{o}C AND heart rate>90 = 1 point (n=20)

- Patients scoring 1 point = 88 comprising 75 (85%) SM and 13 (15%) strokes
- Patients scoring 2 points = 8 comprising 7 (88%) SM and 1 (12%) stroke
- Patients scoring 1 or 2 points = 96 comprising 82 (85%) SM and 14 (15%) stroke

This generated a collection of characteristics for inclusion in a SM identification tool which are summarised in table 1.5.10.

Table 1.5.10 Characteristics considered for SM identification tool			
Characteristic	**Stroke**	**SM**	**OR (95% CI)**
Age<40 years	5	23	7.1 (2.7-18.7)
PMH epilepsy AND seizures	1	15	22.9 (3.0-174.1)
PMH migraine AND headache	4	12	4.6 (1.5-14.2)
Unconscious AND headache WITHOUT facial weakness	0	9	15.1 (1.9-118.8)*
SBP<95mmHg	3	12	6.7 (1.9-23.6)
Temperature>38.0^{o}C AND heart rate>90bpm	2	18	14.3 (3.3-61.7)

*Approximated by adding 1 to each variable

Despite 'Unconscious and headache without facial weakness' being a good predictor of SM diagnosis, this combination of characteristics did not have the same clinical meaningfulness or biological plausibility as the other characteristics i.e. it did not point towards an obvious SM diagnosis. This combination of variables also included headache which was already present in the migraine and headache combination. Therefore this combination was excluded from the final version.

1.5.8 The STEAM tool

1.5.8.1 Model specification

The final iteration of the initial SM tool is described below in table 1.5.11, with STEAM chosen as the acronym. If a suspected stroke patient possessed any of these five characteristics then the tool was judged positive and the patient had a high chance of being a SM. The tool was simple, based on five characteristics that are commonly available in the pre-hospital setting, and critically it identified SM with a high level of specificity.

Table 1.5.11 Characteristics included in the STEAM SM identification tool

Characteristic	Stroke	SM	OR (95% CI)
SBP<95mmHg	3	12	6.7 (1.9-23.6)
Temperature>38.0^{o}C AND heart rate>90bpm	2	18	14.3 (3.3-61.7)
Epilepsy AND seizures at onset	1	15	22.9 (3.0-174.1)
Age<40 years	5	23	7.1 (2.7-18.7)
Migraine AND headache at onset	4	12	4.6 (1.5-14.2)

1.5.8.2 Model performance

Based upon the 1,650 suspected stroke patients transported by NEAS to NHCT over three years, including 989 (60%) stroke and 661 (40%) SM, the STEAM tool retrospectively identified 90 patients: 76 (84%) SM and 14 (16%) strokes. The diagnostic performance of the STEAM tool was calculated as follows:

- Sensitivity 11.5% (9.2-14.2)
- Specificity 98.6% (97.6-99.2)
- Positive predictive value (PPV) 84.4% (75.6-90.5)
- Negative predictive value (NPV) 62.5% (61.8-63.2)
- Positive likelihood ratio (PLR) 8.1 (4.6-14.2)
- Negative likelihood ratio (NLR) 0.9 (0.9-0.9)
- Odds ratio (OR) 9.3 (5.2-16.7)

The STEAM positive patients are reported in table 1.5.12 based on the number of STEAM characteristics they triggered.

Table 1.5.12 STEAM positive patients displayed by number of positive characteristics			
STEAM positive characteristics	**Stroke**	**SM**	**Total**
1	13	72	85
2	1	4	5

The five patients who triggered two STEAM characteristics were all positive for age, three were positive on migraine plus headache and two were positive on epilepsy plus seizures. The STEAM false positive (stroke patient) triggered on age and migraine plus headache.

The patients who were STEAM false positives (i.e. true stroke patients identified as SM by the STEAM tool, n=14) were traced back to the original SSNAP data to establish the rate of reperfusion treatment. Thrombolysis had been administered to three (21%, 1 x SBP<95mmHg, 1 x age<40, 1 x migraine and headache) of these patients.

STEAM performance was also reported based on FAST status. The relationship between FAST and the STEAM tool is explored further in chapter 2.2 where the initial STEAM tool is refined.

Table 1.5.13 STEAM positive patients in FAST+ve and FAST-ve populations			
FAST status	**Stroke**	**SM**	**Total**
Positive (n=1,520)	14	65	79
Negative (n=130)	0	11	11

1.5.9 Discussion

The STEAM tool achieved simple and specific SM identification. It was developed using unfiltered pre-hospital data to ensure applicability in the pre-hospital setting. The concept of clinically meaningful combinations and 'simple and specific' guided the choice of predictor variables for inclusion in the final tool. STEAM identified a small proportion of the SM population with a high level of certainty.

STEAM includes similar variables to other SM identification tools as reported in table 1.1.5 in chapter 1.1. The five variables included in STEAM identify different populations of SM

patients, although a small number (n=5) of patients trigger multiple STEAM characteristics. The individual STEAM characteristics are discussed below.

1.5.9.1 Systolic blood pressure

SBP is a common measurement in pre-hospital care and is easily monitored either manually or using an automatic non-invasive blood pressure cuff, which most ambulances carry. SBP<95mmHg is a relative hypotension especially in the context of stroke which is commonly associated with hypertension (Appleton *et al.*, 2016).

Hypotension is rare in stroke patients (~5%, (Leonardi-Bee *et al.*, 2002)) but hypotension can lead to syncope which is a recognised SM (Gibson and Whiteley, 2013). The mechanisms underlying syncope are usually either orthostatic hypotension or vasovagal, either of which can lead to reduced cerebral perfusion (Shukla and Zimetbaum, 2006). Reduced cerebral perfusion caused by hypotension can produce stroke-like symptoms such as:

- dizziness / vertigo
- slurred speech
- visual disturbances
- motor weakness
- cognitive impairment

Hypotension, or the absence of hypertension, is included as a predictive factor for SM in three existing SM tools (Hand *et al.*, 2006; Ali *et al.*, 2014; Goyal *et al.*, 2016b).

1.5.9.2 Temperature and heart rate

These two variables are easily measured in the pre-hospital setting and commonly recorded as part of the basic observations completed on all patients. Individually, a raised temperature nor a raised heart rate discriminate between stroke and SM, but in combination they point towards an underlying infection or sepsis. Sepsis or the presence of infection can present with stroke like symptoms or lead to decompensation in patients with a previous stroke. Sepsis was the third most frequently reported SM by Gibson and Whiteley (Gibson and Whiteley, 2013).

A raised temperature and heart rate are included in the NEWS as physiological markers of illness and the SIRS criteria for identifying patients with an infection or sepsis (Comstedt *et*

al., 2009). Matching the NEWS and SIRS criteria should facilitate use of STEAM as the trigger points are consistent across the assessment tools.

1.5.9.3 Epilepsy and seizures

A seizure or seizures can lead to stroke like symptoms and a condition known as Todd's paresis. This is a recognised phenomenon where patients present with symptoms such as weakness, slurred speech or a focal neurological deficit in the postictal phase following a seizure (Werhahn, 2010). Many pre-hospital stroke pathways have seizures as an indication for transporting the patient directly to the nearest ED as opposed to a stroke unit. The ROSIER stroke identification tool (Nor *et al.*, 2005) included seizures, as well as loss of consciousness, as factors that reduced the probability of final stroke diagnosis.

Seizures were the most common SM identified by Gibson and Whiteley and the most common level 2 CCS diagnostic group in the literature review (chapter 1.2). Seizures in isolation were associated with SM diagnosis and seizures when combined with PMH epilepsy were the strongest predictor (based on OR) in STEAM. Seizures are included in three existing SM tools (Chang *et al.*, 2012; Ali *et al.*, 2014; Goyal *et al.*, 2016b).

1.5.9.4 Age

Age is included in four of the SM identification tools described in chapter 1.1 (Merino *et al.*, 2013; Ali *et al.*, 2014; Goyal *et al.*, 2016b; Siddiqui *et al.*, 2016). The association between increasing age and increased risk of stroke is well documented (Asplund *et al.*, 2009). Although young age is a strong epidemiological predictor of SM diagnosis in the data and identifies a large number of SM there is a risk associated with dismissing stroke symptoms in individual patients purely based on age. The inclusion of age is discussed further in the focus groups described in chapters 2.1 and 3.3. Recent campaigns have sought to increase the awareness of stroke in the younger population, which could change the balance between stroke and SM presentations.

1.5.9.5 Migraine and headache

Headache was the fourth most common SM documented by Gibson and Whiteley and the second most common level 2 CCS diagnostic group described in chapter 1.2. In the data presented headache in isolation was not a strong predictor of SM diagnoses. PMH migraine

was more predictive than headache, but in a similar fashion to temperature and heart rate the two factors combined were strongly predictive and had a biologically plausible explanation for stroke like symptoms due to a SM condition.

Headache is not an unusual symptom during stroke (Tentschert *et al.*, 2005) but it is also the main symptom of migraine and is present in many other SM conditions (Devenney *et al.*, 2014). Hemiplegic migraine is a rare condition which presents with single sided weakness which is a classic stroke symptom. This condition could be misdiagnosed as a stroke and potentially thrombolysed.

1.5.9.6 Interpretation

STEAM was developed from pre-hospital data with the principles of simplicity and specificity guiding the development process. These factors should increase the probability that STEAM is applicable in the pre-hospital setting. The dataset used to create STEAM was large (n=1,650) compared to other SM tool cohorts (chapter 1.1) but with a higher SM rate (40%) than would have been expected based on the literature (chapter 1.2).

The process of creating STEAM moved through three stages, from an all-encompassing regression model, through a more focussed model and concluded with a simple but specific combined model. This represented an iterative development process as insight was gained into the range of SM conditions and the limitations of the pre-hospital data. In developing a clinical prediction tool the aim is to maximise both sensitivity and specificity, which was attempted by the initial regression model. In many cases sensitivity and specificity have an inverse relationship at the level of maximum test performance, i.e. one is gained at the expense of the other. Specificity was more important in the development of the SM tool so a low sensitivity was accepted. In other settings, such as during telephone triage or in-hospital, a different balance of priorities will be present. Telephone triage prioritises high sensitivity in order to detect the maximum number of potential stroke cases, whereas in-hospital decision making, supported by advanced neuro-imaging, can strive for maximum sensitivity and specificity.

STEAM is the only SM tool designed for pre-hospital use and derived from pre-hospital data so comparisons to other SM tools need to take this into account. STEAM has a lower

sensitivity but a similar specificity to other tools reporting these performance characteristics (Libman *et al.*, 1995; Goyal *et al.*, 2016b).

1.5.9.7 Implications

STEAM achieved the stated aim which was to develop a simple but specific tool that could be used in the pre-hospital setting to identify SM patients. STEAM now needs to be refined and validated in new datasets as this is only the first stage of the development process. The potential clinical uses, such as diversion away from a stroke unit, and acceptability to stakeholders need to be explored.

The implications of introducing STEAM on a large scale can be considered based on the performance characteristics described. If the following basic assumptions are made:

- 100,000 strokes in the UK in a single year.
- 75% of stroke patients are identified and admitted by ambulance.
- 40% SM rate in ambulance admissions.

Then there would be 75,000 stroke admissions and 50,000 SM admissions per year by ambulance. If STEAM detects 12% of SM patients with 84% PPV then it will identify 7,142 patients, 6,000 will be SM and 1,142 will be false positive (true stroke) patients. This basic modelling of the impact of STEAM will be developed and expanded upon in chapter 3.2.

STEAM has demonstrated one possible outcome of linking pre-hospital stroke data with in-hospital diagnoses. There are many other potential uses for this type of linked dataset. Further research in this area could examine how STEAM could be applied in practice, the high SM rate in this cohort, how paramedics are identifying stroke patients with reference to the FAST+ve and FAST-ve populations and what are the implications of using it in combination with the increased sensitivity gained by expanding the criteria for stroke identification such as the FAST-AVVV (ataxia, vomiting, vertigo, visual deficit) tool being using by one UK ambulance service (Roberts-Andreou, 2016).

1.5.9.8 Limitations

The methods used to develop the STEAM tool were based on an iterative and intuitive process that combined regression analysis with information gained from multiple sources and the clinical insight of the author and supervisory team. The method might be difficult to

replicate as STEAM was not derived purely from the regression analysis and the process included a number of assumptions based upon clinical experience, but these will be explored during the professional focus groups described in chapter 2.1. The focus on simplicity limited the amount of variables that were considered for combination in this work whereas a more sophisticated electronic tool, or use in a less time pressured setting, would enable more variables and a more complex tool to be constructed.

The retrospective nature of the data introduced limitations in terms of data quality from a lack of complete recording of items of interest. Information that may have been of interest, such as psychiatric history, was not easily available within the dataset. Gargalas et al identified two groups of SM patients; medical and functional/psychiatric (Gargalas *et al.*, 2017). STEAM focussed on the medical group of SM patients due to the lack of psychiatric data in the pre-hospital records and the lack of expertise paramedics have in psychiatric assessment.

It is important to recognise that this dataset reflected spontaneous assessment and clinical record keeping by ambulance clinicians who were not routinely required to document STEAM clinical characteristics. Therefore, STEAM might perform differently if completion was mandatory. The hospital diagnoses were also based on retrospective records so the outcome of interest, stroke or SM, may not have been considered at the time therefore patients will have undergone differing assessment processes. A prospective study of STEAM would need to ensure complete recording of relevant variables on all patients and consistent assessment in hospital to allow more robust analysis and evaluation.

There were varying amounts of missing data in the physiological variables. An imputation method could have been used to replace the missing data items but most methods would have imputed values close to the mean which would not have affected the development of STEAM as only abnormal values are discriminatory.

Pain was the characteristic with the most missing data, but it was not included in the final tool due to low specificity and little biological plausibility. Temperature was the only other characteristic with less than 95% completeness (87%) and it was included in STEAM. When the patients with missing temperature values (n=216) were examined only 64 (4% of total) had a heart rate>90. Only 2% of all patients had a temperature>38.0^{o}C so it appears unlikely

that any imputation method would have caused many of this group of patients to trigger STEAM.

Some predictor variables identified by the analysis and chosen for inclusion were only recorded in a small number of patients. This may be due to the variables only being present in the small number or they may not have been considered as relevant at the time.

STEAM was derived from data from a single hospital so the sample may not be representative of all pre-hospital stroke patients. Expanding the dataset to include other sites would address this limitation.

1.5.10 Conclusions

This chapter described the development of the initial SM identification tool. The final version was the STEAM tool which includes five characteristics that identify a small number of SM with a high level of certainty. STEAM meets the aim of developing a simple but specific SM identification tool. The iterative development process was guided by analysis of pre-hospital data linked with patient diagnoses. The survey of paramedics and a systematic review of the literature also contributed to the development process.

1.5.11 Summary

Development of the STEAM tool concludes part 1 of this thesis. The next stages are reported in part 2 of the thesis and include focus groups with professional stakeholders (paramedics and hospital clinicians) to explore their views about the STEAM tool, refinement of the STEAM tool using an expanded dataset, and prospective testing of the STEAM tool by NEAS paramedics to generate data on its usability.

Chapter 2.0 Summary of part 1 and overview of part 2

Part 1 of this thesis described the initial idea, literature review, survey and development dataset that led to the creation of the SM tool v1 (STEAM). Figure 1.0.2 from chapter 1.0 is reproduced below to illustrate the overall research process.

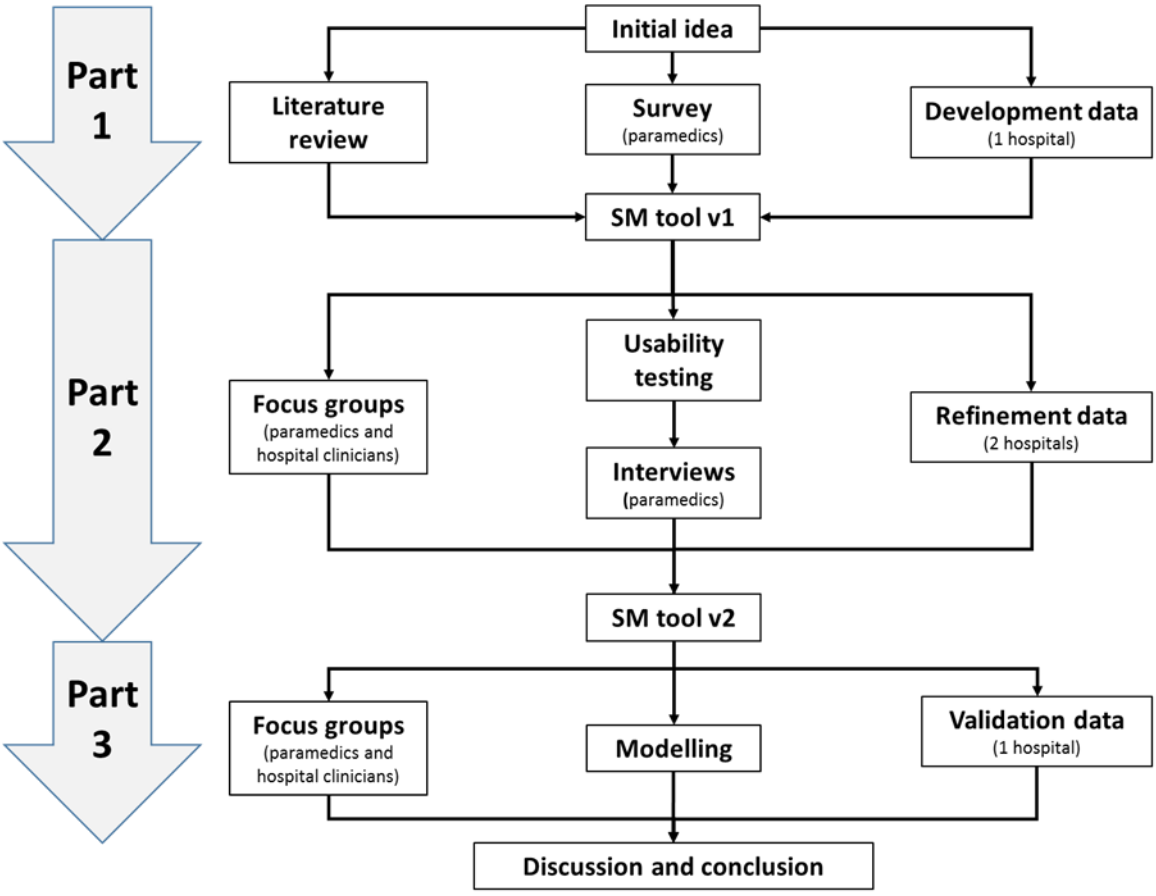


Figure 1.0.2 Flowchart with overview of pre-hospital SM project

Part 2 builds on the STEAM tool that was developed in part 1. Chapter 2.1 describes the findings from focus groups with paramedics and hospital clinicians exploring their views on the acceptability of STEAM, how it could be improved and the implications of using STEAM in practice.

STEAM is refined in chapter 2.2 based on the findings of the focus groups and expansion of the patient dataset with the addition of data from two additional acute trusts. This expanded the dataset from 1,650 to 3,797 suspected stroke patients which allowed more precise estimation of predictive variables.

Chapter 2.3 reports on the prospective use of STEAM by NEAS paramedics, in order to explore its usability and how it could be incorporated into current practice. This prospective testing was conducted using mixed methods. The culmination of the results reported in part 2 of the thesis is a refined STEAM tool with qualitative data in support of its usability and acceptability in practice.

Chapter 2.1 Professional stakeholder views on the STEAM tool

2.1.1 Introduction

Following the development of STEAM, described in part 1, views from relevant professional stakeholders about its perceived acceptability in the clinical setting were sought. This chapter describes the design, data collection and findings of a qualitative study exploring professional stakeholder views on the development of STEAM.

This is the first of three phases of qualitative work that were conducted to inform the development of STEAM and explore healthcare professional views about applying the tool in practice. The second and third qualitative phases are described in chapters 2.3 and 3.3.

2.1.2 Chapter aim

The aim of this chapter is to report the views of healthcare professionals, who have experience and interest in pre-hospital and acute stroke care, regarding the development, structure and content of STEAM.

2.1.3 Methods

2.1.3.1 Design

A generic qualitative approach (Cooper and Endacott, 2007; Griffiths and Mooney, 2011) was selected due to the inexperience of the researcher and the multi-methods nature of the wider project.

Focus groups were chosen as an appropriate method for data collection. Barbour (Barbour, 2008) (p8) described how focus groups are useful in health services research as the perspectives of relevant parties can assist with the development of effective interventions. A focus group allows participants with varying roles and responsibilities to discuss the issue of interest and the interaction between the participants provides insights that would be difficult to gain using other methods. Focus groups were appropriate as they allowed participants, selected for their experience in acute stroke care, to express and discuss their views on SM and the STEAM tool. This data would then be used to inform the development and refinement of STEAM.

2.1.3.2 Participants

Participants were sought from relevant professional stakeholders including paramedics, stroke physicians, ED physicians and stroke nurse practitioners in one acute trust (NHCT) and one ambulance trust (NEAS). These groups were targeted as representative of professionals with clinical responsibilities where a SM tool might impact upon practice. The aim of the focus groups was to gain insight into the development and future deployment of STEAM so a convenience sample was used. Participants were considered representative of their professions. No specific eligibility criteria were applied other than participants had to be employed by NEAS or NHCT and involved in providing acute stroke care. Participants were recruited by advertising for volunteers within the respective organisations and attendance at existing meetings where relevant professionals were present. All participants were supplied with information sheets regarding the study prior to the focus groups. Informed written consent was gained at the start of each focus group after participants had a chance to ask questions.

The aim was to recruit 4-6 participants per focus group based on the recommendations of Barbour (Barbour, 2008) (p60) and Pope and Mays (Pope and Mays, 2006) (p26). These numbers would ensure a variety of views were represented, there were enough participants to promote discussion and the group was manageable by the single facilitator.

2.1.3.3 Data collection and analysis

Separate focus groups were organised for the paramedics and the hospital staff. This was done in order to focus on the views of each professional group, as opposed to the interaction between the groups, and to avoid any perceived authority of one group over the other. As the aim was to seek clinical insight for the development and future deployment of the SM tool there was no expectation of reaching data saturation with only two focus groups.

A topic guide was used for both focus groups (see appendix H). The topic guide was developed by the researcher and the supervisory team, informed by relevant literature and covered broad areas such as the development of STEAM, application and barriers or facilitators to use. The guide was intended to help keep the groups focussed on the issues of interest whilst allowing unexpected areas of discussion to arise.

Stimulus material (see appendix I) was used in the form of a short summary of the findings from the literature review, the background to the study along with the STEAM tool and descriptors of its performance in terms of sensitivity, specificity, positive and negative predictive values. This was given to all participants to stimulate views and to act as reference material during the discussion.

Brief field notes were taken during the focus group and used by the researcher to ensure key points were covered and interesting points that arose were investigated without interrupting the flow of conversation.

Digital audio recordings were made of the focus groups. The audio recordings were transcribed verbatim by the researcher and anonymised for the purpose of analysis. Thematic analysis was conducted using a five stage framework as described by Pope and Mays (Pope and Mays, 2006) (p72-74). This approach is described as suitable for applied research with predetermined topics and outcomes, in this case views about STEAM and its structure/content. The five stages of thematic analysis applied to the data are summarised below:

- Familiarisation. Immersion in the data by transcription, reading and listening to recordings.
- Identification of thematic framework. Key issues, themes and concepts identified.
- Indexing. Coding of data.
- Charting. Grouping of data according to themes.
- Mapping and interpretation. Explanation of findings based on original question.

In practice this involved repeatedly reading through the original transcripts and listening through the original recordings to ensure a good overview of the discussions was gained. After this the transcripts were examined line by line to identify any themes of interest. Themes were identified based on the a priori topics documented in the topic guide along with other issues that appeared relevant to the development of the STEAM tool. Once these initial themes were identified then they were combined and grouped based on similar content, issue or meaning. This involved a measure of interpretation and going back to the original transcripts to examine the context for some themes to ensure they were being interpreted and grouped appropriately. The charting and mapping stages involved testing for

patterns and overlap between data in various combinations and establishing whether there were links between identified themes, and groups of themes, in a way which reflected the original views of the participants.

2.1.3.4 Approvals

Approvals for all three phases of qualitative work were secured at the same time as this was considered one extended project running throughout the SM tool development study. Ethical approval for the qualitative phases of the study was gained from Newcastle University Faculty of Medical Sciences Ethics Committee (ref 01203/2016). Health Research Authority (HRA) approval was gained as this project included staff selected due to their positions in the NHS across multiple trusts (ref 207285). This project was adopted onto the National Institute for Health Research (NIHR) Clinical Research Network (CRN) portfolio (ref CPMS 32323). All approvals related to the qualitative work can be found in appendix J.

2.1.4 Findings

Focus group 1a (FG1a) was conducted at NHCT and lasted 31 minutes. There were nine participants comprising five stroke consultants; one ED consultant; two stroke nurse practitioners and one medical student. Focus group 1b (FG1b) was conducted at NEAS and lasted 57 minutes. There were three participants comprising three senior paramedics.

The two focus groups were conducted on consecutive days. This meant that structured analysis of the first focus group was not completed prior to the second focus group. Topics raised during the first focus group were noted by the researcher and influenced the second focus group.

Data from the two focus groups is presented in a combined fashion due to the common themes that emerged. Seven interconnected themes were identified which are displayed in figure 2.1.1. The themes are described in more detail below with illustrative anonymised quotes to enhance credibility. NHCT participants are indicated by N1-9 and FG1a. NEAS participants are indicated by P1-3 and FG1b.

Figure 2.1.1 Themes from phase 1 focus groups

2.1.4.1 Actions based on STEAM

Actions that could be triggered by STEAM were discussed within both focus groups. This key theme highlighted the importance of developing clear guidance for ambulance staff in response to the STEAM result:

> *"So I suppose it's what do you do with that patient when you've come to the end of this process, so you identify you think it's a mimic, what are we going to do with that patient?" P1, FG1b*

This was closely linked to how STEAM would interact with the stroke identification tools, primarily FAST, currently used by the ambulance service:

> *"If you're negative FAST would you do STEAM anyway?" P1, FG1b*

There was discussion around what would be considered to be the most appropriate destination and who should make the stroke or SM decision. Current practice in most North East hospitals is for suspected stroke patients to be transported to specialist stroke services, whereas other conditions are primarily admitted via ED. The NEAS focus group could see the benefits from using STEAM to allow ambulances to deviate from this pathway for SM in terms of reduced journey times, reduced use of secondary ambulances for repatriation and an increased accuracy for initial diagnosis:

> *"I think from a paramedic point of view it's a good idea, I think it's a good idea from the patients point of view because you know right care right treatment and they're getting treated for something that potentially isn't a stroke anyway so I think there's an issue there but I think as we move more to centralised hyper acute strokes then we're taking people significant distance further for potentially for something that they don't need to be taken for and I think we're missing therefore what is wrong with them" P1, FG1b*

The difference between paramedic and non-paramedic crews was discussed within the NEAS focus group. There was a general view that STEAM could be used by non-paramedic crews. This led on to a discussion about whether suspected stroke patients needed paramedic input, as ambulance services utilise a variety of staff with varying levels of clinical responsibility in order to provide all emergencies with rapid assessment. There is a move towards a more targeted approach in order to make more efficient use of limited or specialist resources for specific patient groups i.e. critical care teams with pre-hospital physicians are targeted at life threatening conditions where they can provide time critical interventions.

This was a point of interest from a service provision perspective as ambulance clinicians currently deliver no treatment specifically for stroke. The primary function of the ambulance clinician is to identify the patient as a suspected stroke and transport them safely to the most appropriate receiving unit which is achievable by paramedics and non-paramedics. There were conflicting views about this shared role within the ambulance service focus group. One participant highlighted the enhanced assessment skills and greater underpinning knowledge of paramedics as well as the potential for patients to deteriorate and need paramedic interventions:

"I think one of the problems with strokes is that they're often looked at as being low risk, but I've seen stroke patients deteriorate and arrest" P2, FG1b

One key insight which came from the ambulance service focus group was that the idea of STEAM was unusual in pre-hospital care in that it is a 'rule out' as opposed to a 'rule in' tool. Pre-hospital care tends to be conservative and err on the side of caution, it is unusual to rule something out once it is initially suspected:

"There may be some challenges because we've always worked on a ruling in system" P2, FG1b

The hospital response to the introduction of STEAM was discussed at greater length in the hospital focus group. The discussion focussed upon the potential for STEAM to help prioritise resources and organise the appropriate response to a SM, which was supported by stroke services and ED staff:

"So then the question becomes prioritisation within the ED service itself" N1, FG1a

It was also recognised that STEAM could be used by non-stroke service staff in hospital such as junior doctors or ED triage nurses:

"I have to say from our junior point of view I would say anyone who comes in who is FAST positive it's like oh my god it's a stroke and sometimes there's not really the thought process about what else" N4, FG1a

There was a feeling that STEAM was more useful in the pre-hospital setting where it would be more likely to affect the actions taken. However, pre-hospital services need to communicate with hospital services using common terminology so actions based on STEAM need to be considered across services:

"A conversation is a two person thing so the other person on the end of the conversation has to understand," N4, FG1a

2.1.4.2 Triggering and improving communication

A SM tool has the potential to trigger or improve communications. This was discussed at greater length in the hospital focus group than the ambulance focus group. The potential to use STEAM to trigger a conversation between the ambulance crew on scene and the

receiving stroke team was considered a more acceptable use of STEAM than it being used to determine the patient's destination without input from the receiving clinicians:

> *"It just needs to be coupled with a discussion somewhere along the lines, isn't it, especially in that situation where you're going to potentially go somewhere different." N4, FG1a*

The potential for STEAM to provide structured content within the information passed to the hospital via a pre-alert was discussed. Pre-alerts trigger a hospital response according to the information contained, whether this is a single message passed via ambulance control to the hospital or whether this is a direct clinician to clinician discussion:

> *"It may have impact from an A&E point of view as stroke get pre-alerted, if you say I'm happy this is a stroke mimic that would maybe mean less pre-alerts" N4, FG1a*

A tool like STEAM would allow a direct conversation to be structured. A structured conversation encourages collection of the relevant data and eases the communication of information in a scenario where efficiency is beneficial. This would be an indirect benefit of introducing a tool like STEAM.

2.1.4.3 Decision making process

Decision making was a key theme that linked closely with the actions, risk and the differential diagnosis themes (see below). Decision making incorporates multiple facets such as how the SM decision is made, how decision making could be supported and who is responsible for the decision. Both focus groups were concerned by who should be making the decision about probable SM and considered whether stroke physician input was required.

However, there was an argument put forward, primarily in the NEAS discussion, that STEAM could support and empower ambulance crew decision making, and that the best person to make the decision was the person face to face with the patient at the scene. The discussion about who should make the decision was very closely linked to who had responsibility for the patient:

> *"Have a conversation with the stroke unit and get the stroke unit to make the decision" P1, FG1b*

"But I think it would be difficult to put the responsibility of calling it a stroke mimic onto the paramedics if it then turns out to be something else" N2, FG1a

The topic of support for making these decisions, both at the time and afterwards, if they proved to be mistaken was discussed:

"It's about making sure that that's (acceptance of risk) communicated out to staff so that they feel supported and they don't feel isolated in their decision making" P3, FG1b

There was discussion within the hospital focus group about whether there should be some consideration of time since onset of symptoms and therefore potential eligibility for thrombolysis in the application and decision making based upon STEAM.

"You have to consider thrombolysing them if they come in within the time limit" N2, FG1a

There was recognition that time elapsed affects the way that stroke patients are treated and also that mechanical thrombectomy was on the horizon which may have a longer treatment window than thrombolysis although there will still be the need to get suspected stroke patients assessed as soon as possible.

The decision making process for patients who are clearly unwell was discussed and the opinion within the NEAS focus group was that individual clinicians have to make the best decision for the patient at that time. The exclusion of patients with GCS<8 from STEAM removed one group of unwell patients, and if there were other reasons to be concerned about immediate risks then it is hoped that paramedics would always act in the best interests of the patient.

FAST was discussed, particularly within the ambulance service focus group, and how this guides pre-hospital decision making. It was recognised that FAST is established in ambulance service practice, which is supported by the survey results in chapter 1.3, and has been for a number of years:

"FAST is very ingrained into practice and is seen as being, you know, sacred" P2, FG1b

The introduction of any assessment which alters the decision making resulting from the FAST, which STEAM may do, is likely to be challenged or ignored, and deployment will have to overcome cultural hurdles:

> *"You're not going to change people's perception of FAST are you, so, sorry P3, so you're not going to then, the cultural bit's really important as they've always done FAST." P1, FG1b*

However, there was recognition that ambulance crews sometimes suspect a patient is a SM, but treat the patient as a stroke due to organisational protocols and a lack of other options:

> *"I mean this may support people as well because it's often that you will get FAST positive patients who you don't think are having a stroke, but they are FAST positive and you're using sort of clinical intuition that you don't think it's a stroke, you've taken that history but they're still FAST positive and currently you are then going to treat them as a potential stroke patient when you don't believe they are." P2, FG1b*

STEAM would support the clinical intuition, assessment or experience of these paramedics and support their decision making with a recognised tool if introduced.

2.1.4.4 Differential diagnoses for stroke mimics

Both focus groups recognised that the patients in question were not going to be referred on to another care provider or left at home. These patients were going to be transported to hospital, but which hospital, which ward and with what level of urgency depends on the assessment and the initial diagnosis made by the ambulance crew. It was recognised that there are a number of differential diagnoses for these patients, including stroke, and that the underlying condition may not be immediately obvious.

The ambulance service focus group strongly supported the idea of adding in some measure of blood sugars, as an indicator of a hypoglycaemic episode, into STEAM. The absence of this was also noted in the hospital focus group:

> *"Why's blood glucose not in there?" N2, FG1a*

> *"I'm surprised BM isn't in there" P3, FG1b*

BM is a common abbreviation used to refer to a blood sugar reading (Bannister, 2013). Measuring BM is part of the existing NEAS stroke pathway, and is included in most pre-hospital stroke pathways. Low BM, hypoglycaemia, is a recognised SM that paramedics can identify and address, however it is not always completed in practice.

Mental health issues are a common SM and there was discussion about whether STEAM could include some way of identifying this group of SM. It was recognised that these can be a difficult group to rapidly diagnose and that mental health assessment is something that ambulance crews may struggle with in the setting of a suspected acute stroke:

> *"Our history taking about psychiatric and mental health conditions isn't necessarily as strong as it is when we're looking at physical health conditions" P3, FG1b*

One common item of discussion in both focus groups was the importance of taking a good history as this is the only way that factors indicative of a patient being a SM would be identified. The inclusion of items of past medical history in two of the STEAM criteria made this a very relevant issue:

> *"It relies on them being fairly compos mentis or somebody else telling you the information" P2, FG1b*

2.1.4.5 Implementation across trusts

How STEAM could be implemented was a theme that both focus groups touched on. There was concern from the ambulance focus group about the potential for hospital stroke services to want differing actions based upon the SM tool. Organisations could have different risk thresholds and this would need to be addressed. There was a strong feeling that a tool with consistent actions would be easier to implement. Ambulance crews are a mobile workforce and anything which requires a different response based on either time or geography would be more challenging to implement:

> *"So if you're doing a stroke patient in Gateshead at 11 o clock then a stroke patient in South Tyneside at 3 o clock I'd like you to be able to use the same tools and to do the same with the patient" P1, FG1b*

There was recognition that any SM tool would need to be integrated into existing pathways of care and that this would work best if done at a regional level. The importance of involving

regional networks in the introduction and implementation of a SM tool was recognised by both focus groups. UK ambulance services cover large regions and interact with multiple acute trusts, therefore regional introduction would be the only logical way to implement a tool like this.

The ambulance focus group raised a concern about performance metrics and how the introduction of a SM tool would impact on ambulance stroke related, and more general, targets:

> *"At the moment the national measure is for FAST positive patients taken to hospital within the 60 minutes, we would need to take something forward that recognised that FAST positive patients could be stroke mimics and therefore should be excluded from that group of patients when we are considering ultimately what happens to them, otherwise potentially as an ambulance service your performance could potentially be woefully inadequate" P3, FG1b*

2.1.4.6 Risk vs benefit for patients

The potential risks associated with introduction of STEAM were discussed at length in both focus groups. The potential benefits of introducing STEAM were mentioned but did not receive the same level of discussion. Risk stratification was brought up by the ED representation and how STEAM could aid the ED by prioritising patients:

> *"It's part of risk stratification isn't it, it doesn't make the final decision for you" N4, FG1a*

There was concern over the potential for STEAM to mean stroke patients potentially eligible for thrombolysis would miss the opportunity and a strong desire from the stroke physicians to see patients within the treatment window. The risk of younger patients having access to specialist treatment delayed was particularly concerning:

> *"They're the ones that hit, because, you know, they've still got 60 years left of their life or 80 years left of their life because they're really young" P1, FG1b*

The inclusion of age as a factor in STEAM was of concern to both focus groups as patients could be identified as SM based solely on age as opposed to any clinical characteristics or observations:

"I mean you wouldn't want people who had a stroke who just happened to be 39 not to be offered thrombolysis because they were inevitably STEAM positive" N5, FG1a

2.1.4.7 Further developing STEAM

The hospital focus group largely accepted STEAM in its current form whereas the ambulance service focus group were more interested in the development process. The suggestion of including some measure of blood sugar, mentioned earlier, came from both focus groups.

There was the suggestion from the ambulance service focus group of combining STEAM with FAST, or another stroke identification tool, to create a single stroke tool rather than having two separate tools. This was suggested to reduce confusion but went against the opinion that FAST was so well established that any change to FAST would need to be done at a national level. There was acknowledgement that it was beyond the scope of this work to reinvent FAST, and it was more flexible for clinical adoption to have a SM tool that could follow different stroke identification instruments.

Using an electronic platform to facilitate STEAM use was discussed and was felt to be a good way to overcome some of the challenges identified:

"Electronically you could do that, we could build this all in so you get FAST positive then you could come up with a box saying what's the BP, have you checked the BM" P1, FG1b

The implication was that a tool like STEAM could be automated so that when relevant observations were documented in the electronic record it would automatically recognise that STEAM either needed completing or had been triggered. This would remove the need to remember STEAM or check values against printed tables and would potentially improve documentation.

2.1.5 Discussion

This first phase of qualitative work reports the views of paramedics, stroke and ED clinicians regarding STEAM. A number of interrelated issues have been described that emerged from the discussions including what should be done with a STEAM positive patient, who makes this decision, the implications, and how STEAM could be developed and implemented. The focus groups provided useful insight into how STEAM would be received by clinicians and

how it could be developed further to enhance its acceptability and integration into existing assessment processes.

Other studies describing the development of SM tools have not reported any qualitative input into the process (Merino *et al.*, 2013; Ali *et al.*, 2014; Goyal *et al.*, 2016b). However, stakeholder input during the development process is valuable for creating a usable and useful tool (Barbour, 2008) (p8) as was demonstrated during the creation of the COMPASS tool for decision making in stroke thrombolysis (Flynn *et al.*, 2015).

The development and content of STEAM generated few expressions of concern, apart from the age criteria. Age has long been recognised as an important risk factor for stroke. Sacco stated *"Age is the single most important risk factor for stroke."* (Sacco, 1997). Age has been used as a criterion in other SM tools and also as an exclusion from stroke identification tools, most notably the LAPSS which excluded patients under 45 years (Kidwell *et al.*, 2000). Although the age criterion in STEAM has a similar odds ratio to the migraine criterion, is a strong predictor in the development data and is well documented as a differential factor in the literature, as shown in chapter 1.2, concerns were raised during both focus groups about missing a young presentation of stroke.

Age is distinct from the other STEAM criteria as it doesn't point towards another diagnosis, and purely reflects demographic risk. Young patients (defined as age<50 years) account for 10% of ischaemic stroke patients with the incidence rate rising steeply above 40 years (Putaala, 2016). Younger stroke presentations are also diagnosed late due to atypical presentations, lack of classical risk factors and the influence of age upon the wider differential diagnoses (Kuruvilla *et al.*, 2011). Although there is a lower probability of stroke, the more challenging diagnosis and discomfort for clinicians believing that they might be denying a younger stroke patient the opportunity for expedited care meant that the continued inclusion of age was given careful consideration.

The inclusion of blood sugars is a prudent suggestion for improving STEAM as hypoglycaemia is a recognised SM commonly seen in pre-hospital care (Walker, 2011). Measuring blood sugar is part of national ambulance stroke guidelines (Association of Ambulance Chief Executives and Joint Royal Colleges Ambulance Liaison Committee, 2016) but is not explicitly

included in either the FAST or STEAM tool. If an algorithm including FAST and STEAM was strictly followed, then measuring blood sugar could be forgotten.

The risk of applying STEAM in practice was covered by both focus groups. The focus was on the risk of a stroke being incorrectly classified as a SM and the potential to delay treatment i.e. thrombolysis. The risks to SM patients treated with thrombolysis has been documented, and although very low, should be avoided if possible (Winkler *et al.*, 2009; Zinkstok *et al.*, 2013; Tsivgoulis *et al.*, 2015).

The lack of evidence, at this stage of the project, as to the potential benefits of identifying SM made it difficult to discuss the wider advantages from deployment. The potential benefits were commented on in terms of better risk stratification, improved communications and more targeted use of resources. The impact on resources was discussed by the hospital clinicians in terms of providing an appropriate response to an ambulance pre-alert and how many staff and what grade of staff to allocate to these calls. The impact on ambulance resources was more focussed around getting the right patient to the right hospital, similar to the model used for major trauma and heart attacks, and avoiding secondary transfers. Clarification of the potential impact of introducing a tool like STEAM will be explored in greater depth in chapter 3.2.

The actions that could be linked to STEAM were discussed at length in both groups and connected with the other themes that emerged. Who should make the final decision that a suspected stroke is actually a SM was a point of disagreement between the groups. The most appropriate action that should be taken with a suspected SM was discussed at length and raised the possibility of having different actions linked to different triggering criteria. The action agreed upon by both focus groups was to use STEAM to trigger communication between pre-hospital and stroke services.

Overall the focus groups provided valuable contextual insight that informed the further development of STEAM. The two groups expressed some similar views such as: support for the concept; benefits of communication; concern over age; and also some diverging views such as who should make the SM decision. Due to the lack of literature describing professional's views on SM tools these insights provide essential guidance for developing STEAM and identify challenges that may be encountered if STEAM was to be implemented.

2.1.5.1 Strengths and limitations

The focus group participants were all relevant professionals with an interest in stroke care. The results of the focus groups provided useful insight into STEAM content and development, suggestions to potentially improve the acceptability and performance of the tool and opinions about barriers and facilitators to its use in practice. The findings are limited by the fact that both groups work in the same region, although participants in both groups had knowledge of pathways and practices outside of this region.

The small numbers attending the ambulance service focus group were disappointing although it was never the aim to describe views representing the breadth of the service. In focus groups there is the risk of strong personalities or characters dominating the discussion and leading others towards their viewpoint. The ambulance service participants all contributed equally towards the discussion and were well known to each other despite their different roles. The paramedics may have been biased towards supporting STEAM as they were all volunteers. The physicians dominated the hospital based focus group. Due to the number of physicians within the group there was still a useful discussion, with some input from the other healthcare professionals involved in emergency stroke patient assessment.

2.1.6 Conclusions

The views collected during the focus groups were valuable for considering how STEAM could be developed and deployed to enhance acceptability.

This phase of qualitative data collection has resulted in a number of key points that were considered during the further development of STEAM.

- Inclusion of BM.
- The acceptability of an age criterion.
- The actions that STEAM will trigger.

2.1.7 Summary

The qualitative information described in this chapter provides valuable insight to complement the additional clinical information reported in the next chapter, and the usability testing, which is reported in chapter 2.3. Collectively these three stages informed the revised STEAM tool that was developed.

Chapter 2.2 Refinement of the STEAM tool

2.2.1 Introduction

STEAM was developed using data from 1,650 suspected stroke patients transported by NEAS to a single hospital (NHCT). This chapter describes the impact of adding data from 2,147 additional suspected stroke patients collected at another two hospital trusts. This created a larger dataset which was used to refine the STEAM tool. The refinement process was also informed by the findings from the focus groups reported in the previous chapter.

2.2.2 Chapter aims and objectives

The aim of this chapter is to describe the refinement of the STEAM tool.

The objectives are to:

- Describe a refinement dataset combining suspected stroke patients transported by NEAS to three acute trusts in the North East.
- Refine STEAM using the dataset and the focus group findings from chapter 2.1 with the intention of developing a simple and specific tool.

2.2.3 Background

The basic method for developing a clinical prediction tool, based on Adams & Leveson (Adams and Leveson, 2012) and Moons et al (Moons *et al.*, 2009b), was outlined in chapter 1.1 and included four basic steps:

1. Development of a tool that identifies the condition of interest.
2. Validation that the tool performs as expected in a new population.
3. Impact analysis of what difference the tool would make in practice.
4. Implementation of the tool into regular healthcare.

Step 1 was completed with the development of the STEAM tool. Instead of moving straight to validation work (step 2) extra data was first collected in the form of a refinement dataset which enabled STEAM to be improved before validation work was undertaken.

Refinement was undertaken for the following reasons:

- Although a regional pre-hospital dataset had been created, STEAM was developed on data from a single hospital trust. The refinement process used data from three hospital trusts which reduces any biases introduced by the standards, processes or practices in a single trust.
- To account for demographic or population differences due to hospital catchment areas.
- To utilise the increased dataset to consider the predictive value of individual variables with greater power.
- To increase the generalisability of the STEAM tool.

The development of STEAM, reported in chapters 1.4 and 1.5, was completed before access to the diagnoses data used to create the refinement dataset was available. The staggered access to hospital diagnoses data allowed methods and processes to be tested and refined on a single trust (NHCT) before they were applied in additional settings.

2.2.4 Methods

The refinement dataset was created using the same methods as the development dataset described in chapter 1.4 which are summarised below:

- Suspected stroke patients transported by NEAS were identified.
- Data on variables relevant to stroke or SM diagnoses were collected from NEAS.
- NEAS suspected stroke patients were linked with hospital SSNAP and HES records to establish discharge diagnoses.

Following advice from statisticians within Newcastle University, STEAM was refined using an iterative process based on the development methods reported in chapter 1.5:

- The performance of STEAM was tested using the refinement dataset.
- Univariate analysis of variables in the refinement dataset in order to increase the precision of previously established predictive variables and see if any new predictive variables emerged.
- Clinically logical combinations of variables were explored for meaningful predictors of SM diagnoses.

- STEAM was refined based upon clinician feedback (reported in chapter 2.1) and analyses of the refinement dataset.

This process was undertaken to refine and improve the previously developed STEAM tool. Major alterations were only considered if there was significant variation in the predictive value of individual variables.

2.2.4.1 Setting

Data were collected from two additional acute hospital trusts in the North East.

The first was Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH), which serves Newcastle upon Tyne. NUTH admitted 748 confirmed stroke patients in 2016/17. NUTH consistently performs well in the SSNAP audit in criteria relevant to this work, such as case ascertainment where it scored 90%+ from 2014 onwards (RCP, 2017b).

The second was North Tees and Hartlepool NHS Foundation Trust (NTEES) which admits stroke patients in the south of the region covered by NEAS. NTEES provides care to around 400,000 people living in Hartlepool, Stockton and County Durham. NTEES admitted 576 confirmed stroke patients in 2016/17. NTEES consistently performs well in the SSNAP audit in criteria relevant to this work, such as case ascertainment where it scored 90%+ from 2014 onwards (RCP, 2017b).

2.2.4.2 Timeframe

Data were collected over the same three year timeframe as the development cohort i.e. 01/06/2013 to 31/05/2016.

2.2.4.3 Data extraction, linkage and analysis

Extraction, linkage and analysis of all data followed the same processes described in chapter 1.4. All data were extracted into Excel and imported into SPSS for analysis.

2.2.4.4 Approvals

Local approvals were secured from all participating trusts for data sharing.

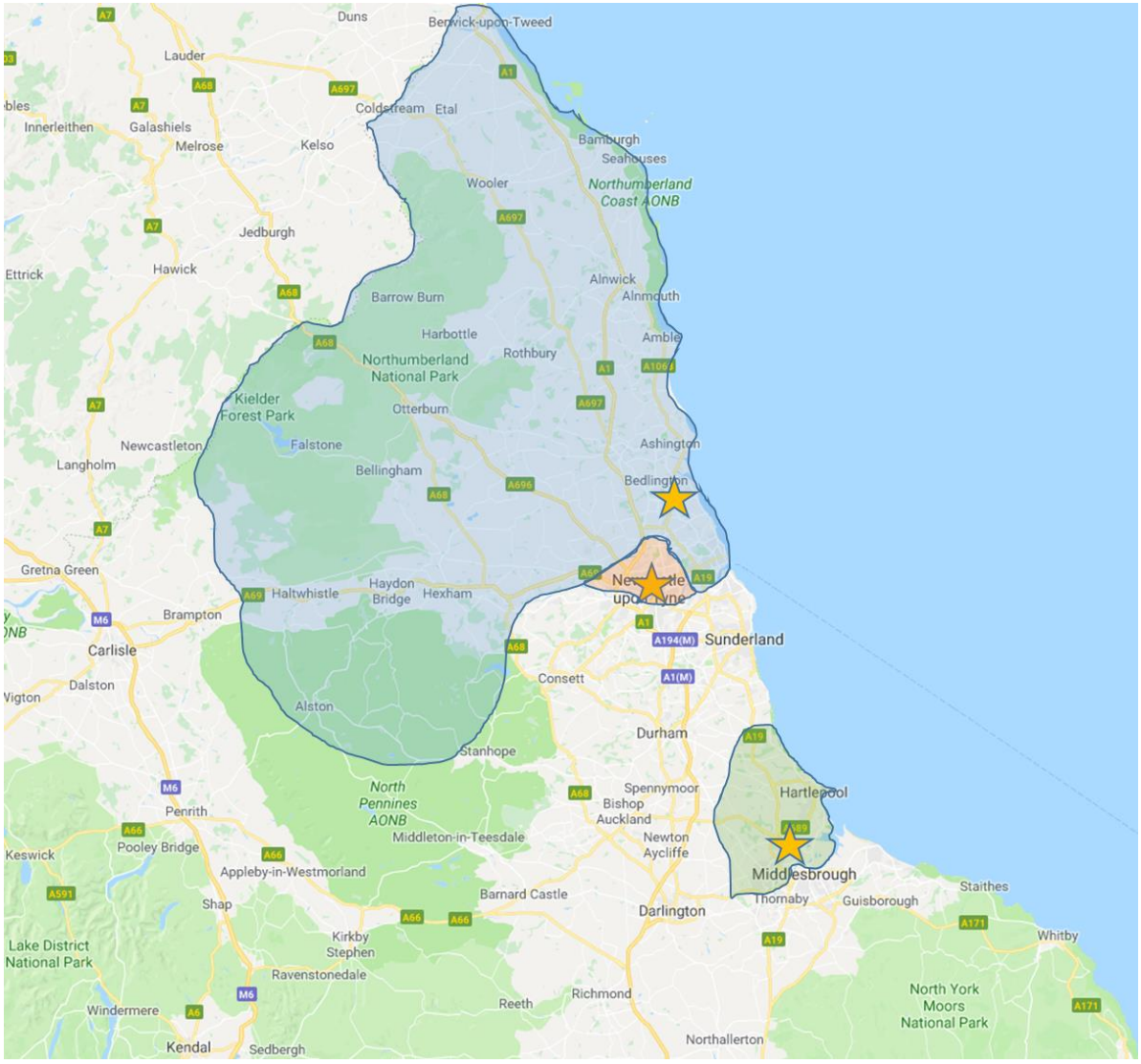


Figure 2.2.1 Map of the North East with NHCT (top), NUTH (middle) and NTEES (bottom) approximate catchment areas

2.2.5 Results

The 1,650 suspected stroke patients transported to NHCT have already been described in chapters 1.4 and 1.5.

NEAS transported 1,000 suspected stroke patients to NUTH, including 38% SM. Full details of the NUTH cohort can be found in appendix K.

NEAS transported 1,147 suspected stroke patients to NTEES, including 45% SM. Full details of the NTEES cohort can be found in appendix L.

The refinement dataset therefore included 3,797 suspected stroke patients of which 2,240 (59%) were stroke and 1,557 (41%) were SM.

2.2.5.1 Patient demographics

The demographics of the suspected stroke cohorts are displayed in table 2.2.1. All patients had gender recorded. Twenty-six patients had no age documented but were included as they were recorded as adults.

Table 2.2.1 Demographics of NEAS suspected stroke patients reported by discharge diagnosis

		Suspected stroke	Stroke	SM	P value
NHCT (development cohort)	**Patients**	1,650	989	661	-
	Mean age (SD)	75.3 (13.4)	77.0 (11.7)	72.8 (15.3)	<0.001
	Gender (% male)	47%	50%	41%	<0.001
NUTH	**Patients**	1,000	618	382	-
	Mean age (SD)	73.5 (14.6)	75.3 (12.8)	70.8 (16.9)	<0.001
	Gender (% male)	48%	50%	46%	0.060
NTEES	**Patients**	1,147	633	514	-
	Mean age (SD)	71.3 (14.9)	73.8 (13.0)	68.1 (16.5)	<0.001
	Gender (% male)	49%	49%	49%	0.982
Refinement dataset	**Patients**	3,797	2,240	1,557	-
	Mean age (SD)	73.6 (14.3)	75.6 (12.4)	70.8 (16.2)	<0.001
	Gender (% male)	48%	50%	44%	0.001

Stroke patients were significantly older (independent samples t-test, $p<0.001$) than SM patients across all trusts. SM were significantly more likely to be female in the development and refinement datasets (chi squared test) but not in the NUTH and NTEES individual hospital cohorts.

2.2.5.2 Source of diagnoses of suspected stroke patients

The source of the diagnoses for the NEAS suspected stroke patients transported to the three hospitals in the refinement dataset are reported in table 2.2.2.

Table 2.2.2 Source of diagnoses for suspected stroke patients in the refinement dataset				
	NHCT	**NUTH**	**NTEES**	**Total**
Suspected stroke patients	**1,650**	**1,000**	**1,147**	**3,797**
Stroke based on SSNAP	839 (85%)	527 (85%)	547 (86%)	1,913 (85%)
Stroke based on HES	66 (7%)	52 (8%)	45 (7%)	163 (7%)
TIA based on HES	84 (8%)	39 (6%)	41 (6%)	164 (7%)
Total Stroke (inc TIA)	**989**	**618**	**633**	**2,240**
SM based on HES	526 (80%)	306 (80%)	158 (31%)	990 (64%)
Assumed SM	135 (20%)	76 (20%)	356 (69%)	567 (36%)
Total SM	**661**	**382**	**514**	**1,557**

Note. Percentages refer to the percentage of the relevant diagnostic group (stroke or SM) for each hospital i.e. 85% of stroke diagnoses in NHCT were based on SSNAP.

2.2.5.3 Assumed SM patients

SM patients were identified by either confirmed non-stroke diagnosis (any ICD-10 code other than I61, I63, I64 or TIA codes G458 and 459) in hospital HES systems or assumed based upon an inability to match with either SSNAP or HES. The assumed diagnoses group are likely to reflect patients that were assessed and treated in ED but were not admitted. Patients with an assumed SM diagnosis are compared with patients with a confirmed SM diagnosis in table 2.2.3 below.

Table 2.2.3 Comparison of patients with confirmed SM diagnoses versus assumed SM diagnoses			
	Diagnoses	**Age (mean, SD)**	**Gender (% Male)**
NHCT (n=661)	**Confirmed (n=526)**	74.0 (14.7)	41
	Assumed (n=135)	67.5 (17.4)	41
NUTH (n=382)	**Confirmed (n=306)**	71.1 (16.2)	44
	Assumed (n=76)	68.5 (21.1)	41
NTEES (n=514)	**Confirmed (n=158)**	68.0 (16.4)	49
	Assumed (n=356)	68.2 (16.6)	49
Refinement dataset (n=1,557)	**Confirmed (n=990)**	72.2 (15.6)	43
	Assumed (n=567)	68.3 (17.0)	46

The NHCT confirmed and assumed SM patients were significantly different in age (independent samples t-test, p=<0.001) but not gender (chi square test, p=0.977).

The NUTH confirmed and assumed SM patients were not significantly different in age (independent samples t-test, p=0.323) or gender (chi square test, p=0.565).

The NTEES confirmed and assumed SM patients were not significantly different in age (independent samples t-test, p=0.917) or gender (chi square test, p=0.965).

SM patients in the refinement dataset with confirmed and assumed SM diagnoses were significantly different in age (independent samples t-test, p=<0.001) but not significantly different in gender (chi square test, p=0.302).

2.2.5.4 SM diagnoses

Two hundred and fifty-seven different ICD-10 diagnostic codes were recorded for the 990 patients with a confirmed SM diagnosis.

The ICD-10 based SM diagnoses are displayed in table 2.2.4.

Table 2.2.4 Most frequent ICD-10 diagnoses recorded for combined SM patients		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
N390	Urinary tract infection, site not specified	66 (7%)
R55X	Syncope and collapse	55 (6%)
R568	Convulsions, not elsewhere classified	55 (6%)
R298	Other symptoms and signs involving the nervous and musculoskeletal systems	46 (5%)
G409	Epilepsy, unspecified	33 (3%
J181	Lobar pneumonia, unspecified organism	30 (3%)
G510	Bell's palsy	25 (3%)
G439	Migraine, unspecified	24 (2%)
G819	Hemiplegia, unspecified affecting unspecified side	18 (2%)
J22X	Unspecified acute lower respiratory infection	18 (2%)
F059	Delirium, unspecified	17 (2%)
R478	Other speech disturbances	17 (2%)
R296	Repeated falls	16 (2%)
C793	Secondary malignant neoplasm of brain and cerebral meninges	15 (2%)
R51X	Headache	15 (2%)
I620	Nontraumatic subdural hemorrhage	13 (1%)
R410	Disorientation, unspecified	13 (1%)
R208	Other disturbances of skin sensation	11 (1%)
I951	Orthostatic hypotension	10 (1%)
J189	Pneumonia, unspecified organism	10 (1%)
N179	Acute kidney failure, unspecified	10 (1%)
Other	Other conditions with less than 1% (n=10) prevalence	473 (48%)

The ICD-10 codes were summarised using Clinical Classification Software (CCS) codes. The most frequent SM diagnoses represented using level 2 CCS codes are shown in table 2.2.5.

Table 2.2.5 Combined SM diagnoses displayed using level 2 CCS codes		
CCS level 2 code	**CCS description**	**Number (%) of patients**
6.4	Epilepsy; convulsions	106 (11%)
6.9	Other nervous system disorders	100 (10%)
10.1	Diseases of the urinary system	79 (8%)
13.8	Other connective tissue disease	78 (8%)
17.1	Symptoms; signs; and ill-defined conditions	62 (6%)
6.5	Headache; including migraine	59 (6%)
8.1	Respiratory infections	46 (5%)
7.3	Cerebrovascular disease	44 (4%)
5.4	Delirium dementia and amnestic and other cognitive disorders	27 (3%)
7.2	Diseases of the heart	27 (3%)
7.4	Diseases of arteries; arterioles; and capillaries	22 (2%)
6.3	Paralysis	20 (2%)
8.8	Other lower respiratory disease	20 (2%)
2.12	Secondary malignancies	16 (2%)
2.11	Cancer; other primary	14 (1%)
NR	Not recorded	14 (1%)
3.8	Fluid and electrolyte disorders	13 (1%)
5.11	Alcohol-related disorders	13 (1%)
1.1	Bacterial infection	12 (1%)
2.3	Cancer of bronchus; lung	12 (1%)
6.8	Ear conditions	11 (1%)
2.14	Neoplasms of unspecified nature or uncertain behaviour	10 (1%)
9.1	Intestinal infection	10 (1%)
16.4	Intracranial injury	10 (1%)
Other	Other conditions with less than 1% (n=10) prevalence	165 (17%)

The CCS codes were combined into level 1 CCS codes to show broader clinical groupings as shown in table 2.2.6.

Table 2.2.6 Combined SM diagnoses displayed using level 1 CCS codes		
CCS1 code	**CCS code description**	**Number (%) of patients**
1	Infectious and parasitic diseases	16 (2%)
2	Neoplasms	68 (7%)
3	Endocrine; nutritional; and metabolic diseases and immunity disorders	29 (3%)
4	Diseases of the blood and blood-forming organs	4 (<1%)
5	Mental Illness	50 (5%)
6	Diseases of the nervous system and sense organs	320 (32%)
7	Diseases of the circulatory system	96 (10%)
8	Diseases of the respiratory system	83 (8%)
9	Diseases of the digestive system	24 (2%)
10	Diseases of the genitourinary system	79 (8%)
11	Complications of pregnancy; childbirth; and the puerperium	1 (<1%)
12	Diseases of the skin and subcutaneous tissue	6 (1%)
13	Diseases of the musculoskeletal system and connective tissue	89 (9%)
16	Injury and poisoning	46 (5%)
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	65 (7%)
18	Residual codes; unclassified; all E codes	14 (1%)

The combined SM diagnoses are graphically displayed in figure 2.2.2 with figure 1.2.3 from the systematic review repeated below for comparison.

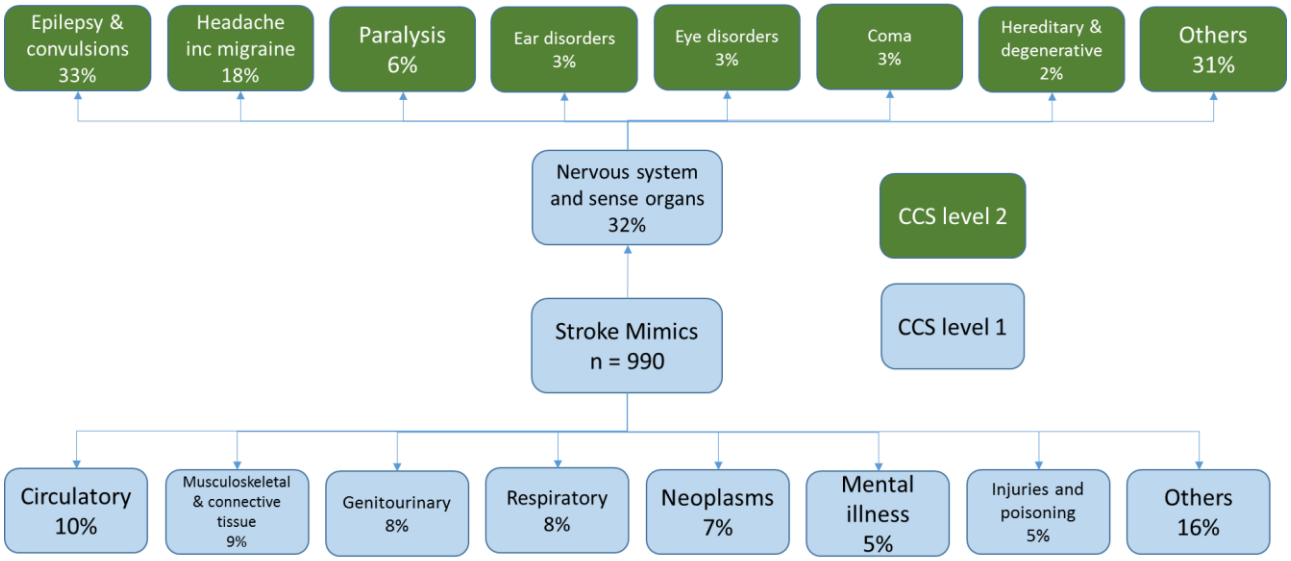


Figure 2.2.2 Combined SM diagnoses summarised using CCS codes

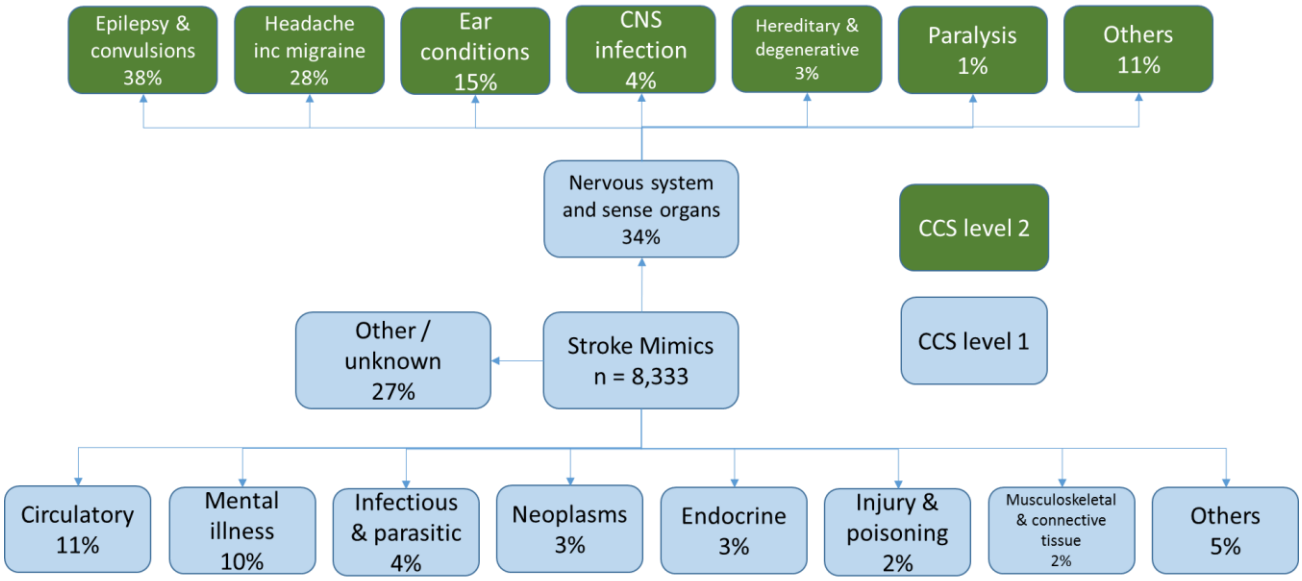


Figure 1.2.3 Taxonomy of SM using CCS codes (repeated from chapter 1.2)

2.2.5.5 Comparison of SM diagnoses across hospital trusts

The percentage of each level 1 CCS SM diagnoses are displayed by individual hospital trust included in the refinement dataset below.

Table 2.2.7 Contributing trusts SM diagnoses % displayed using level 1 CCS codes				
CCS1 code	**CCS code description**	**NHCT**	**NUTH**	**NTEES**
1	Infectious and parasitic diseases	2%	1%	2%
2	Neoplasms	6%	10%	3%
3	Endocrine; nutritional; and metabolic diseases and immunity disorders	3%	3%	1%
4	Diseases of the blood and blood-forming organs	0%	0%	1%
5	Mental Illness	5%	6%	4%
6	Diseases of the nervous system and sense organs	31%	29%	41%
7	Diseases of the circulatory system	9%	11%	8%
8	Diseases of the respiratory system	9%	8%	8%
9	Diseases of the digestive system	2%	3%	3%
10	Diseases of the genitourinary system	9%	6%	8%
11	Complications of pregnancy; childbirth; and the puerperium	0%	0%	0%
12	Diseases of the skin and subcutaneous tissue	1%	0%	1%
13	Diseases of the musculoskeletal system and connective tissue	8%	9%	11%
16	Injury and poisoning	5%	6%	2%
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	7%	6%	8%
18	Residual codes; unclassified; all E codes	1%	3%	0%

2.2.5.6 Physiological observations

The physiological observations recorded from suspected stroke patients in the refinement dataset are displayed in table 2.2.8 below.

Table 2.2.8 Physiological observations in NEAS data on suspected stroke patients in the refinement dataset reported by discharge diagnosis				
Physiological observations	**n (%) of patients with observation documented**	**Stroke (mean, SD)**	**SM (mean, SD)**	**P value (stroke vs SM)**
BM (mmol/l)	3,639 (96)	7.6 (2.8)	7.4 (2.7)	0.032
GCS	3,797 (100)	14 (1.9)	14 (1.9)	0.878
Heart rate	3,791 (99)	82 (18.7)	84 (19.3)	0.003
Irregular pulse	3,690 (97)	25%	17%	<0.001
Pain (0-10)	2,452 (65)	0.3 (1.1)	0.6 (1.7)	<0.001
SaO2	3,770 (99)	96 (2.6)	96 (3.2)	0.191
Respiratory rate	3,793 (99)	17 (3.0)	17 (3.0)	0.142
SBP (mmHg)	3,772 (99)	161 (28.6)	154 (29.0)	<0.001
DBP (mmHg)	3,763 (99)	89 (17.3)	87 (18.5)	0.015
Temperature (Celsius)	3,300 (87)	36.5 (0.7)	36.6 (0.9)	<0.001

2.2.5.7 Past medical history

The PMH of suspected stroke patients in the refinement dataset are shown in table 2.2.9 below.

Table 2.2.9 Past medical history of suspected stroke patients in the refinement dataset reported by discharge diagnosis				
	n (%) of total patients with condition	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value (stroke vs SM)**
PMH Alcohol misuse	61 (2)	25 (1)	36 (2)	0.004
PMH Angina	322 (9)	191 (9)	131 (8)	0.902
PMH Diabetes	615 (16)	384 (17)	231 (15)	0.058

Table 2.2.9 Past medical history of suspected stroke patients in the refinement dataset reported by discharge diagnosis				
	n (%) of total patients with condition	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value (stroke vs SM)**
PMH Epilepsy	157 (4)	56 (3)	101 (6)	<0.001
PMH Heart failure	97 (3)	72 (3)	25 (2)	0.002
PMH High cholesterol	614 (16)	372 (17)	242 (16)	0.381
PMH Hypertension	1172 (31)	757 (34)	415 (27)	<0.001
PMH MI	348 (9)	217 (10)	131 (8)	0.181
PMH Migraine	51 (1)	17(1)	34 (2)	<0.001
PMH Smoking	78 (2)	48 (2)	30 (2)	0.644
PMH Stroke	937 (25)	468 (21)	469 (30)	<0.001
PMH TIA	596 (16)	325 (15)	271 (17)	0.016

2.2.5.8 Clinical signs and symptoms

The signs and symptoms recorded by the paramedics are displayed below.

Table 2.2.10 NEAS observations on suspected stroke patients in the refinement dataset reported by discharge diagnosis				
	n (%) of total patients with condition	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value (stroke vs SM)**
Abnormal gait	355 (9)	238 (11)	117 (8)	0.001
AF	362 (10)	258 (12)	104 (7)	<0.001
Alcohol/Drug use reported	100 (3)	41 (2)	59 (4)	<0.001

Table 2.2.10 NEAS observations on suspected stroke patients in the refinement dataset reported by discharge diagnosis

	n (%) of total patients with condition	Stroke (% of stroke patients with condition)	SM (% of SM patients with condition)	P value (stroke vs SM)
Altered Sensation (FT)*	332 (9)	171 (8)	161 (10)	0.004
Arm weakness*	2472 (65)	1637 (73)	835 (54)	<0.001
Chest pain	44 (1)	17 (1)	27 (2)	0.006
Confusion	1109 (29)	613 (27)	496 (32)	0.003
Dizziness	303 (8)	161 (7)	142 (9)	0.031
Eye issues (FT)*	205 (5)	145 (7)	60 (4)	<0.001
Facial droop or weakness	2139 (56)	1383 (62)	756 (49)	<0.001
FAST +ve*	1958 (52)	1242 (55)	716 (46)	<0.001
Floppy	200 (5)	125 (6)	75 (5)	0.3
General weakness	858 (23)	457 (20)	401 (26)	<0.001
Headache	826 (22)	420 (19)	406 (26)	<0.001
Leg weakness*	1772 (47)	1223 (55)	549 (35)	<0.001
Nausea or vomiting*	398 (11)	199 (9)	199 (13)	<0.001
Neck Stiffness	61 (2)	29 (1)	32 (2)	0.067
Seizures	125 (3)	29 (1)	96 (6)	<0.001
Speech symptoms	2607 (69)	1653 (74)	954 (61)	<0.001
Syncope	33 (1)	12 (1)	21 (1)	0.008
Tremors	102 (3)	45 (2)	57 (4)	0.002
Unconscious	167 (4)	63 (3)	104 (7)	<0.001
Visual disturbances*	311 (8)	163 (7)	148 (10)	0.014

*The same criteria for these characteristics were used as described in chapter 1.4

2.2.5.9 Paramedic documentation of clinical impression

"Paramedic impression" was examined to see if it related to discharge diagnosis. Impression was grouped into three distinct categories:

1. Stroke only = stroke as only suspected diagnosis.
2. Stroke and TIA = stroke and TIA documented as only diagnoses.
3. Stroke plus other = stroke included amongst multiple differential diagnoses.

These three categories of impression were then compared with hospital discharge diagnoses.

Table 2.2.11 Paramedic impression and discharge diagnoses in the refinement dataset

Impression	Total patients	Stroke	SM
Stroke only	2,910	1,871 (64%)	1,039 (36%)
Stroke and TIA	299	166 (56%)	133 (44%)
Stroke plus other	588	203 (35%)	385 (65%)

The "stroke plus other" impression category included stroke plus a median of 1 additional impression (range 1-7, IQR 1-2) out of 40 different conditions for stroke patients and 50 for SM.

2.2.5.10 STEAM results in datasets

The results of applying STEAM to the NHCT (development), NUTH, NTEES and refinement datasets are shown below.

Table 2.2.12 Suspected stroke patients displayed by number of STEAM characteristics				
Trust	**Number of positive STEAM characteristics**	**Stroke**	**SM**	**Total patients**
NHCT	0	975	585	1560
	1	13	72	85
	2	1	4	5
NUTH	0	606	337	943
	1	12	43	55
	2	0	2	2
NTEES	0	620	463	1083
	1	13	51	64

Note: STEAM positive rows are shaded.

The results of applying STEAM to the combined refinement dataset are shown in table 2.2.13. STEAM identified 172 SM patients and 39 stroke patients.

Table 2.2.13 STEAM output when applied to refinement dataset			
STEAM score	**Stroke**	**SM**	**Total patients**
0	2,201	1,385	3,586
1	38	166	204
2	1	6	7

Note: STEAM positive rows are shaded.

2.2.5.11 Characteristics triggering STEAM

The STEAM characteristics recorded as present are shown in table 2.2.14.

Table 2.2.14 Characteristics triggering STEAM								
Characteristic	**NHCT Development (n=90)**		**NUTH (n=57)**		**NTEES (n=64)**		**Total Refinement (n=211)**	
	Stroke	**SM**	**Stroke**	**SM**	**Stroke**	**SM**	**Stroke**	**SM**
SBP<95mmHg	3	12	3	5	3	1	9	18
Temperature + HR	2	18	4	8	1	8	7	34
Seizures + PMH Epilepsy	1	15	0	8	1	9	2	32
Age<40	5	23	3	21	6	26	14	70
Headache + PMH Migraine	4	12	2	5	2	7	8	24
Totals*	**14**	**76**	**12**	**45**	**13**	**51**	**39**	**172**

*Note: totals represent total number of patients and do not match the column totals as some patients triggered multiple characteristics.

2.2.5.12 STEAM performance in datasets

The performance characteristics of STEAM when applied to the NUTH, NTEES and refinement datasets using STEAM≥1 to indicate SM are shown in table 2.2.15 compared with STEAM performance in the development dataset.

Table 2.2.15 STEAM performance in NUTH, NTEES and refinement datasets compared with development (NHCT) dataset							
	NHCT	**NUTH**		**NTEES**		**Refinement**	
	Development dataset	**Performance**	**Change**	**Performance**	**Change**	**Performance**	**Change**
Sensitivity (95% CI)	11.5% (9.2-14.2)	12.2% (9.1-15.9)	+0.7%	9.9% (7.5-12.8)	-1.6%	11.1% (9.5-12.7)	-0.4%
Specificity (95% CI)	98.6% (97.6-99.2)	98.1% (96.6-99.0)	-0.5%	98.0% (96.5-98.9)	-0.6%	98.3% (97.6-98.8)	-0.3%
PPV (95% CI)	84.4 (75.6-90.5)	79.7% (67.8-87.9)	-4.7%	79.7% (68.3-87.7)	-4.7%	81.5% (75.8-86.1)	-2.9%

STEAM performed in a consistent manner in terms of sensitivity and specificity in the refinement dataset. However, the PPV of STEAM went down from 84.4% to 81.5%. This reduction in accuracy, and the availability of the extra data in the refinement dataset, led to the components of STEAM being revised in order to improve the predictive performance of the tool.

2.2.6 Refinement of the STEAM tool

It was not surprising that the larger refinement cohort, combining multiple services and populations, resulted in a different predictive performance by STEAM. Further examination of characteristics associated with SM diagnosis was performed in order to consider whether STEAM could be improved. The methods of data analysis were based on those described in chapter 1.5 but the refinement process started with the existing STEAM tool which will be referred to as STEAMv1 from this point.

2.2.6.1 Univariate analysis

Individual variables in the refinement dataset were analysed. ROC analysis was applied to the continuous variables that were significant ($p<0.05$) in univariate analysis to calculate optimum cut-off values. DBP was excluded due to its close relationship with SBP.

Table 2.2.16 ROC analysis of continuous variables in refinement dataset

Variable	Cut-off	P value	Sensitivity	Specificity
Age	<40	<0.001	0.05	0.99
BM	<3.2	0.010	0.00	1
Heart rate	<37	0.002	0.00	1
Pain	>3	0.002	0.09	0.97
SBP	<92	<0.001	0.01	1
Temperature	<29.8	<0.001	0.00	1

All the variables analysed using ROC were significant which may be due to the increased amount of data in the refinement dataset. The following decisions were made about including the following variables in the refinement process:

- Age, pain and SBP did not interact with each other and were included.
- Low heart rate and low temperature were excluded as these extreme values only identified a single patient each.
- The inclusion of BM within the refinement process, based upon feedback from the focus groups reported in chapter 2.1, triggered extensive discussions within the supervisory team. As BM testing exists as a discrete point of care test in most ambulance service clinical pathways, this was made an inclusion criteria for STEAM application. This is discussed further in the STEAMv2 refinement section later in this chapter.

The cut-off values calculated in the ROC analysis were used to dichotomise the continuous variables and calculate OR. The OR for the included variables are shown in table 2.2.17. As the outcome of interest was SM diagnosis an OR>1 was associated with SM diagnosis and OR<1 was associated with stroke diagnosis.

Table 2.2.17 Odds ratios of predictor variables for SM diagnosis in refinement dataset

	Odds ratio	**Lower 95% CI**	**Upper 95% CI**
Age<40	7.5	4.2	13.3
Gender (female)	1.3	1.1	1.4
Physiological observation			
Pain>3	2.8	1.9	4.0
Irregular pulse	0.6	0.5	0.7
SBP<92mmHg	4.1	1.5	11.4
Past Medical History			
Alcohol misuse	2.1	1.3	3.5
Angina	1.0	0.8	1.2
Diabetes	0.8	0.7	1.0
Epilepsy	2.7	1.9	3.8
Heart failure	0.5	0.3	0.8
High cholesterol	0.9	0.8	1.1
Hypertension	0.7	0.6	0.8
MI	0.9	0.7	1.1

Table 2.2.17 Odds ratios of predictor variables for SM diagnosis in refinement dataset cont.			
	Odds ratio	**Lower 95% CI**	**Upper 95% CI**
Migraine	2.9	1.6	5.2
Smoking	0.9	0.6	1.4
Stroke	1.6	1.4	1.9
TIA	1.2	1.0	1.5
Signs and symptoms			
Abnormal gait	0.7	0.5	0.9
AF	0.6	0.4	0.7
Alcohol/Drug use reported	2.1	1.4	3.2
Altered Sensation	1.4	1.1	1.7
Arm weakness	0.4	0.4	0.5
Chest pain	2.3	1.3	4.2
Confusion	1.2	1.1	1.4
Dizziness	1.3	1.0	1.6
Eye issues	0.6	0.4	0.8
Facial droop or weakness	0.6	0.5	0.7
FAST+ve	0.7	0.6	0.8
Floppy	0.9	0.6	1.1
General weakness	1.4	1.2	1.6
Headache	1.5	1.3	1.8
Leg weakness	0.5	0.4	0.5
Nausea or vomiting	1.5	1.2	1.9
Neck Stiffness	1.6	1.0	2.7
Seizures	5.0	3.3	7.6
Speech symptoms	0.6	0.5	0.6
Syncope	2.5	1.2	5.2
Tremors	1.9	1.2	2.8
True FAST-ve	2.0	1.6	2.6
Unconscious	2.5	1.8	3.4
Visual disturbances	1.3	1.1	1.7

The characteristics with the strongest association with SM diagnoses based on the OR were: age<40 (OR 7.5, 95% CI 4.2-13.3); seizures (OR 5.0. 95% CI 3.3-7.6); SBP<92mmHg (OR 4.1, 95% CI 1.5-11.4); and migraine (OR 2.9, 95% CI 1.6-52). The characteristics with the strongest association with stroke diagnoses based on the OR were: arm weakness (OR 0.4, 95% CI 0.4-0.5); leg weakness (OR 0.5, 95% CI 0.4-0.5); and a PMH heart failure (OR 0.5, 95% CI 0.3-0.8).

2.2.7 STEAM refinement version 1.1

The univariate analysis showed that four of the STEAMv1 criteria were still the strongest individual predictors of SM diagnoses based on OR. To maximise predictive value, these were further examined in the refinement dataset.

2.2.7.1 Systolic blood pressure

The magnitude of the association between SBP<95mmHg and SM diagnosis fell from an OR of 6.7 in the development dataset to 2.9 in the refinement dataset. The NTEES cohort was unusual as SBP<95mmHg was more strongly associated with stroke than SM. Analysis of SBP in the refinement dataset indicated that a lower value of 92mmHg was the optimum threshold for classification of stroke versus SM. Applying the principle of "simple and specific", a value of 90mmHg was considered instead of 92mmHg. This would be easier to remember as it features in other areas of pre-hospital practice such as trauma and fluids administration. The threshold of 90mmHg was compared with the previous STEAM development value of 95mmHg, and 85mmHg as an equivalent difference below 90mmHg:

Table 2.2.18 SBP characteristics comparison in the refinement dataset

	Stroke patients	SM patients	OR
SBP<95mmHg	9	18	2.9
SBP<90mmHg	4	11	4.0
SBP<85mmHg	3	7	3.4

For clinical convenience and based on the OR shown in table 2.2.18, SBP<90mmHg was included in STEAMv1.1.

2.2.7.2 Temperature and heart rate

Raised temperature and heart rate were included in STEAMv1 as indicators of infection and sepsis as the potential underlying SM aetiology. In the refinement dataset both of these variables were individually significant in the univariate analysis so the combination of temperature and heart rate was re-examined in the refinement dataset.

In the development dataset temperature and heart rate had a combined OR of 14.3 but in the refinement dataset this fell to 7.2. The patients that were STEAM positive based upon raised heart rate and temperature were examined and it was observed that a large proportion of the STEAM false positives were due to temperature values close to 38.0^{o}C. Raising the temperature criteria to 38.5^{o}C identified 22 suspected stroke patients including 3 stroke and 19 SM patients. This improved the predictive power of this combination of characteristics to an OR of 9.2.

Based on this data and support for identifying patients with suspected sepsis expressed in the focus groups, the combination of raised temperature and heart rate was included in STEAMv1.1 with the heart rate maintained at 90 and the temperature increased to 38.5^{o}C.

2.2.7.3 Epilepsy and seizures

Seizures and PMH epilepsy were each significantly associated with SM diagnoses in the univariate analysis and strong predictors based upon OR (seizures OR 5.0, PMH epilepsy OR 2.7). As a combination this pair was a strong predictor of SM diagnoses in the refinement dataset (OR 23.5) and generated the lowest rate of false positives amongst the original STEAMv1 criteria. Based upon this PMH epilepsy and seizures were included in STEAMv1.1 without alteration.

2.2.7.4 Age

The use of an age criterion in STEAM was challenged during the focus groups, particularly during the hospital focus group. However, in the refinement dataset age<40 was still strongly predictive of SM diagnoses with an OR of 7.5 and it identified nearly half of the SM that triggered STEAM. Based on this performance, age was included in STEAMv1.1 but with the intention to re-consider in the next iteration as described below.

2.2.7.5 Migraine and headache

Headache and PMH migraine were each significantly associated with SM diagnoses in the univariate analysis and strong predictors based upon OR (headache OR 1.5, PMH migraine OR 3.2). As this combination was still a strong predictor of SM diagnoses in the refinement dataset (OR 4.4) and generated a low rate of false positives, it was included unchanged in STEAMv1.1.

2.2.7.6 STEAMv1.1

The first refinement of STEAM changed the SBP and temperature values. The STEAMv1.1 criteria and performance characteristics are summarised below.

Table 2.2.19 STEAMv1.1 criteria and discharge diagnoses

Criteria	Stroke	SM	OR
SBP<90mmHg	4	11	4.0
Temperature>38.5°C AND heart rate>90	3	19	9.2
Seizures + PMH Epilepsy	2	32	23.5
Age<40	14	70	7.5
Headache + PMH Migraine	8	24	4.4

Table 2.2.20 STEAMv1.1 output when applied to refinement dataset

STEAMv1.1 score	Total patients	Stroke	SM
0	3616	2210	1406
1	175	29	146
2	6	1	5

Note: STEAM positive rows are shaded.

A STEAMv1.1 score≥1 identified 181 suspected stroke patients including 30 (17%) stroke patients and 151 (83%) SM patients, representing a 9.7% (95% CI 8.3-11.3%) sensitivity, 98.7% (95% CI 98.1-99.1) specificity and 83.4% (95% CI 77.4-88.1%) PPV.

2.2.8 STEAM refinement version 1.2

When applied to the combined dataset, STEAMv1.1 had lower sensitivity than STEAMv1 with little gain in specificity or PPV. However, the increased dataset now allowed consideration of

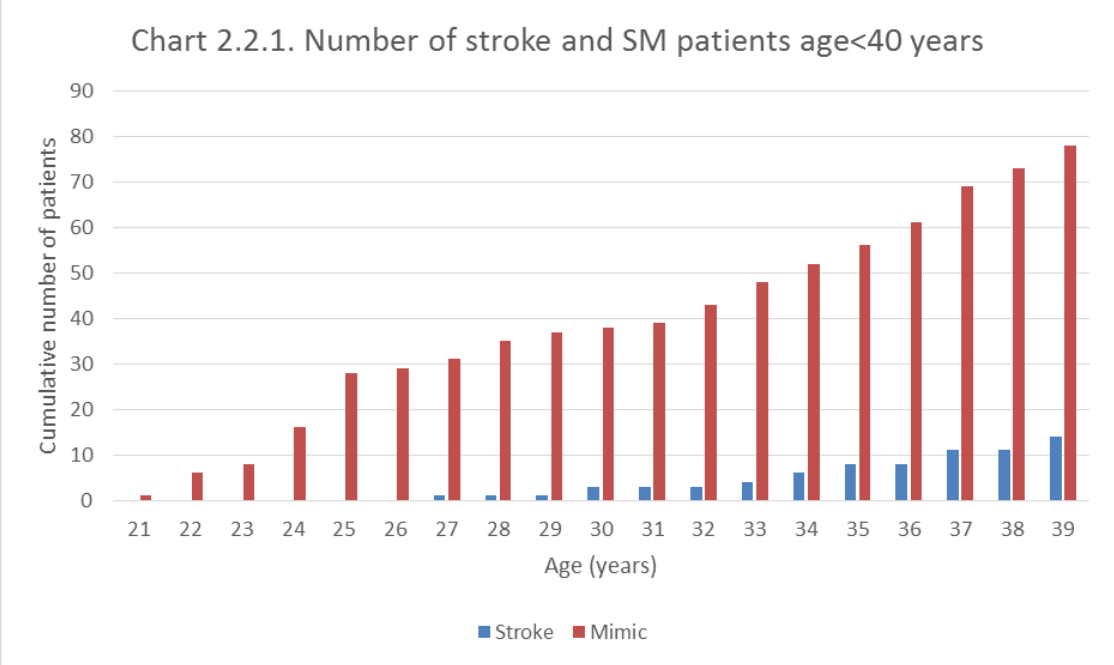
score weighting within specific STEAM characteristics. In order to enhance the specificity and PPV, differential scoring within two characteristics of STEAMv1.1 were considered: age and seizures with PMH epilepsy.

In STEAMv1 and STEAMv1.1 the age criterion generated the largest numbers of stroke and SM patients, but the implications for clinical decision making were questioned in the focus groups (chapter 2.1). Examples of young stroke patients were presented, and clinicians reported feeling uncomfortable with the idea of a patient being classified as a SM based solely on age.

It was apparent that seizures and PMH epilepsy in combination were the strongest predictor by a substantial margin. However other SM tools (described in chapter 1.1) included seizures or history of seizures as individual predictors.

Considering these two criteria, and comments in the focus group likening STEAMv1 to other scores with factor weighting, age and seizures with PMH epilepsy were explored to see if STEAM operational performance could be improved and at the same time address the concerns around the inclusion of age as a binary indicator of SM prediction.

Age<40 years generated high numbers of STEAM+ve patients but also a high proportion of the overall false positives. Chart 2.2.1 displays the number of cumulative stroke and SM patients identified using each age value below 40.



Based on considering this, age as a predictive factor was split into two easy to remember groups reflecting the increasing number of stroke patients from age 30 upwards: age<30 years and age 30-39 years. Age<30 years included 30 suspected stroke patients of which 29 (97%) were SM. Age 30-39 years included 54 suspected stroke patients of which 41 (76%) were SM. With these two groupings identified the age criterion was split so suspected stroke patients received 1 point for age<30 and 1 point for age<40, in effect the patient receives 2 points for age<30 as it triggers both criteria. Therefore a suspected stroke patient aged 28 would receive 2 points whereas a suspected stroke patient aged 35 would only receive 1 point, thus giving greater weight to younger age.

Individually, seizures and PMH epilepsy were each predictive of SM diagnoses (seizures OR 5.0, PMH epilepsy OR 2.7) but the OR for seizures was approximately twice that of PMH epilepsy. Therefore, suspected stroke patients were given 1 point for seizures and 1 point for seizures and PMH epilepsy. This meant that a patient with seizures and PMH epilepsy would receive 2 points.

2.2.8.1 STEAMv1.2

As a result of the analysis and refinement process described above, STEAMv1.2 was created with criteria and predictive performance characteristics summarised below.

Table 2.2.21 STEAMv1.2 criteria and discharge diagnoses

Criteria	Stroke	SM	OR
SBP<90mmHg	4	11	4.0
Temperature>38.5ºC + heart rate>90	3	19	9.2
Seizures	29	96	5.0
Seizures + PMH Epilepsy	2	32	23.5
Age<30	1	29	42.5
Age<40	14	70	7.5
Headache + PMH Migraine	8	24	4.4

For example, a 35 year old suspected stroke patient who presented with a seizure and had a known history of epilepsy would score 3 points (age<40, seizures, seizures + PMH epilepsy). A 28 year old suspected stroke patient with SBP of 85, heart rate 120 and temperature of

39.1°C would score 4 points (age<30, age<40, SBP<90mmHg, temperature>38.5 + heart rate>90).

Table 2.2.22 STEAMv1.2 output when applied to refinement dataset

STEAM score	Total patients	Stroke	SM
0	3528	2183	1345
1	201	53	148
2	63	4	59
3	5	0	5

Note: STEAM positive rows are shaded.

A STEAMv1.2 score≥1 identified 269 suspected stroke patients including 57 (21%) stroke patients and 212 (79%) SM patients, resulting in 13.6% (95% CI 12.0-15.4%) sensitivity, 97.5% (95% CI 96.7-98.1) specificity and 78.8% (95% CI 73.7-83.2%) PPV.

2.2.9 STEAM refinement version 1.3

It was apparent that STEAMv1.2 had increased the sensitivity of STEAMv1 and STEAMv1.1 but with corresponding losses in both specificity and PPV. Sensitivity and specificity normally have an inverse relationship. In this case the performance losses were largely due to the patients scoring 1 on STEAMv1.2. Examining the performance of STEAMv1.2 and the distribution of patients scoring 1-3, the potential to improve the specificity by increasing the predictive threshold from 1 to 2 points was considered.

Raising the threshold needed for STEAM positive status to 2 points identified 68 suspected stroke patients including 4 (6%) stroke patients and 64 (94%) SM patients. Therefore STEAMv1.3 (same criteria as STEAMv1.2 but now requiring 2 points) showed 4.1% (95% CI 3.2-5.2%) sensitivity, 99.8% (95% CI 99.5-99.9%) specificity and 94.1% (95% CI 85.4-97.8%) PPV.

As STEAMv1.3 had good specificity and PPV, but reduced sensitivity, patients that scored 1 point on STEAMv1.2 were examined for any characteristics which could be added to the tool in order to increase the recognition of SM.

Patients who scored 1 point on STEAMv1.2 (n=201) included a high proportion who scored points from seizures (n=88, 27 stroke and 61 SM) and age<40 (n=48, 12 stroke and 36 SM).

These two subgroups also accounted for the majority of the false positives (true strokes) that triggered STEAMv1.2 (n=39, 77%). These cases were examined for characteristics which differentiated the stroke and SM populations. It was apparent that the absence of common stroke symptoms (FAST and leg weakness), was associated with SM diagnoses. The absence of FAST characteristics, and leg weakness, in STEAMv1.2 positive patients who scored 1 point is shown in table 2.2.23.

Table 2.2.23 Absence of FAST characteristics in patients scoring 1 on STEAMv1.2

	Age<40 years (n=48)		**Seizures (n=88)**	
Absent symptom	**Stroke (%)**	**SM (%)**	**Stroke (%)**	**SM (%)**
Face	7 (58%)	21 (58%)	8 (30%)	34 (56%)
Arms	1 (8%)	11 (31%)	8 (30%)	29 (48%)
Speech	2 (17%)	18 (50%)	13 (48%)	36 (59%)
Legs	1 (8%)	20 (56%)	10 (37%)	38 (62%)

Patients without any limb weakness were the group with the fewest false positives and the highest number of SM patients. Leg weakness was closely associated with arm weakness in this group of patients. The 87 patients with arm weakness included 97% of the patients with leg weakness.

If the absence of arm and leg weakness was combined into a new “absence of limb weakness” characteristic to predict SM, then amongst patients who scored 1 point on STEAMv1.2 for either age<40 or seizures this new variable identified 47 suspected stroke patients including 7 (15%) stroke patients and 40 (85%) SM patients.

If this new variable was added into STEAMv1.3 then it produced a more complicated algorithm which is shown below in figure 2.2.3.

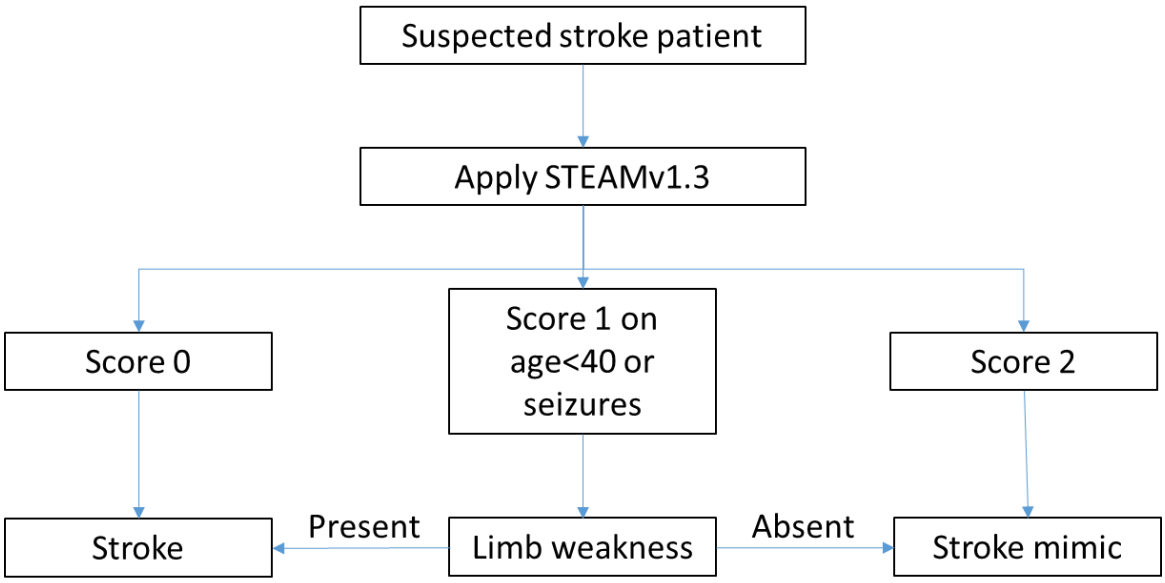


Figure 2.2.3 STEAMv1.3 with added absence of limb weakness characteristic

This version of STEAMv1.3 identified 115 suspected stroke patients including 11 (10%) stroke patients and 104 (90%) SM patients. "STEAMv1.3 + limbs" had 6.7% (95% CI 5.5-8.0%) sensitivity, 99.5% (95% CI 99.1-99.8%) specificity and 90.4% (95% CI 83.6-94.6%) PPV.

Although the performance of STEAMv1.3 + limbs achieved good specificity and PPV it was becoming a more complex process which went against the aim of maintaining simplicity and it was also blurring the intention between stroke and SM identification.

However, limb weakness was based on exploration of the absence of FAST symptoms, and most leg weakness was associated with arm weakness. This led to consideration of incorporating FAST-ve status (reported earlier as True FAST-ve) as a predictor to add into the STEAM refinement process.

FAST-ve (either documented FAST-ve or the absence of any positive FAST symptoms) was a moderate predictor of SM diagnosis in the univariate analysis (OR 2.0). To assist in the identification of SM amongst the subgroup only scoring 1 point on STEAM, but with little positive evidence of stroke symptoms to start with, FAST-ve was added in to STEAMv1.3 as an independent sixth predictor variable scoring 1 point.

The "STEAMv1.3 + FAST-ve" criteria and performance characteristics are summarised below.

Table 2.2.24 STEAMv1.3 + FAST-ve criteria and discharge diagnoses			
Criteria	**Stroke**	**SM**	**OR**
SBP<90mmHg	4	11	4.0
Temperature>38.5^{o}C + heart rate>90	3	19	9.2
Seizures	29	96	5.0
Seizures + PMH Epilepsy	2	32	23.5
Age<30	1	29	42.5
Age<40	14	70	7.5
Headache + PMH Migraine	8	24	4.4
FAST-ve	117	158	2.0

Table 2.2.25 STEAMv1.3 + FAST-ve output when applied to refinement dataset			
STEAM score	**Total patients**	**Stroke**	**Stroke mimics**
0	3283	2070	1213
1	421	162	259
2	84	8	76
3	8	0	8
4	1	0	1

Note: STEAM positive rows are shaded.

STEAMv1.3 + FAST-ve score≥2 identified 93 suspected stroke patients including 8 (9%) stroke patients and 85 (91%) SM patients. STEAMv1.3 + FAST-ve had 5.5% (95% CI 4.4-6.7%) sensitivity, 99.6% (95% CI 99.3-99.9%) specificity and 91.4% (95% CI 83.8-95.6%) PPV.

The results of the refinement process are summarised in table 2.2.26 below.

Table 2.2.26 Summary of STEAM models from refinement process					
	Stroke	**SM**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**
STEAMv1 (development)	14	76	11.5	98.6	84.4
STEAMv1 (refinement)	39	172	11.1	98.3	81.5
STEAMv1.1	30	151	9.7	98.7	83.4
STEAMv1.2	57	212	13.3	97.5	78.8
STEAMv1.3 2 points	4	64	4.1	99.8	94.1
STEAMv1.3 2 points + limbs	11	104	6.7	99.5	90.4
STEAMv1.3 2 points + FAST-ve	8	85	5.5	99.6	91.4

2.2.10 STEAM refinement version 2

In order to retain simplicity of use whilst maximising specificity, STEAMv1.3 (2 points) + FAST-ve was selected as the most suitable version to evaluate as STEAMv2.

Further refinements to STEAMv2 were explored including increasing the SBP to 100mmHg, raising the age<40 criterion to 45 or 49 and inclusion of other characteristics associated with stroke diagnoses such as hypertension, AF and eye symptoms. None of these were judged to improve the performance whilst maintaining the principle of being simple and specific.

The final STEAMv2 tool is:

Target population = suspected stroke patients who are age≥18 with GCS≥8 and BM>3.5.

- SBP<90mmHg = 1 point
- Temperature>38.5^{o}C AND heart rate>90 = 1 point
- Seizures = 1 point
- Seizures AND PMH epilepsy = 1 point
- Age<40 years = 1 point
- Age<30 years = 1 points
- Headache AND PMH migraine = 1 point
- FAST-ve = 1 point

Patients scoring 2 or more points were considered likely SM. STEAMv2 positively identified 93 suspected stroke patients including 8 (9%) stroke patients and 85 (91%) SM patients.

The eight stroke patients incorrectly identified by STEAMv2 (false positives) were identified on the following combinations of characteristics:

- Seizures and FAST-ve = 2 patients
- Seizures AND PMH epilepsy = 2 patients
- Age<40 years and Headache AND PMH migraine = 1 patient
- Headache AND PMH migraine and FAST-ve = 1 patient
- Temperature>38.5^{o}C AND heart rate>90 and FAST-ve = 1 patient
- Age<30 years = 1 patient

The performance characteristics of STEAMv2 were:

- Sensitivity 5.5% (4.4-6.7)
- Specificity 99.6% (99.3-99.9)
- Positive predictive value (PPV) 91.4% (83.8-95.6)
- Negative predictive value (NPV) 60.3% (60.0-60.6)
- Positive likelihood ratio (PLR) 15.3 (7.4-31.5)
- Negative likelihood ratio (NLR) 1.0 (0.9-1.0)
- Odds ratio (OR) 16.1 (7.8-33.4)

2.2.10.1 Sensitivity analysis of assumed SM in STEAMv2

To consider STEAMv2 performance without the uncertainty of cases based on assumed SM diagnoses in the refinement dataset, a sensitivity analysis was performed excluding patients with an assumed SM diagnoses. This resulted in a population of 3,230 suspected stroke patients including 2,240 (69%) stroke patients and 990 (31%) SM patients.

In the sensitivity analysis STEAMv2 score≥2 identified 62 suspected stroke patients including 8 (13%) stroke patients and 54 (87%) SM patients. STEAMv2 had 5.5% (95% CI 4.1-7.1%) sensitivity, 99.6% (95% CI 99.3-99.9%) specificity and 87.1% (95% CI 69.2-72.3%) PPV.

2.2.11 Discussion

The aim of this chapter was to refine STEAMv1 based on the creation of an expanded dataset, informed by the findings of the focus groups reported in chapter 2.1. The iterative process to refine STEAM was guided by the principle of creating a tool that was both simple and specific. Different versions of STEAM were developed with varying combinations of characteristics and consequently operational performance measures. The final iteration (STEAMv2) added FAST-ve to the original five STEAM characteristics and increased the scoring threshold to 2 points. STEAMv2 has a lower sensitivity than STEAMv1 but increases the specificity and PPV.

The creation of the expanded dataset with NUTH and NTEES data provided the opportunity to refine STEAM, which was necessary due to the reduced performance in the refinement dataset. This process allowed STEAM to be developed and refined prior to validation in a further dataset from a fourth hospital which is described in chapter 3.1.

The data from NUTH was similar to the development data from NHCT in terms of demographics. NTEES suspected stroke, diagnosed stroke and SM were younger than the other two trusts and had a slightly different mix of genders. The combination of these different populations should increase the general applicability of STEAM across the NHS.

The SM diagnoses reported using ICD-10 and CCS codes were consistent in the most frequently reported diagnostic groups, i.e. nervous system and sense organs followed by circulatory, and more specific diagnoses, i.e. epilepsy and convulsions followed by headache and migraine. The overall pattern of SM diagnoses was similar to that found in the

systematic review in chapter 1.2. Within the refinement dataset there were lower rates of mental illness, higher rates of musculoskeletal injuries, respiratory and genitourinary CCS codes and slightly different proportions in the most common nervous system CCS codes, i.e. headache and ear conditions. These differences are probably due to the refinement data being based on pre-hospital suspicion of stroke whereas the literature review included all settings. The patterns of SM diagnoses within each contributing trust were similar although NUTH had a higher rate of neoplasm SM and NTEES had a lower rate of injuries and poisonings. These may be due to the small numbers in each group, although in terms of the impact of hospital setting upon the reference standard it is interesting to note that NUTH houses the regional neurosurgical unit and that NTEES is adjacent to a larger NHS trust with a major trauma centre.

Documentation of physiological observations, the FAST test and individual FAST elements were consistent across all three trusts. Pain and temperature were the only physiological characteristics not documented in over 95% of cases. The pattern of PMH presentations was similar across the three trusts with PMH hypertension and PMH stroke being the most commonly reported. These patterns of observations are unsurprising in this pre-hospital suspected stroke population and provide reassurance during the further development of STEAM that the populations from each trust were representative of the pre-hospital suspected stroke population. This is important because if there were unusual or unique features in these populations it could affect the development of the tool and limit the generalisability.

FAST is the standard pre-hospital stroke identification tool in the North East which will have influenced the pre-hospital data and therefore the development, refinement and generalisability of STEAM. If a SM tool were developed in a setting where a different stroke identification tool was used, such as LAPSS, or where additional criteria, such as leg weakness or visual deficit, were already included this would change the tool that was developed. If STEAMv2 were to be applied in a setting where a different stroke identification tool was used it would perform differently. LAPSS excludes seizures and age<45 years so two of the STEAMv2 criteria would be redundant.

The addition of FAST-ve as a criterion was the most obvious change between STEAMv1 and STEAMv2. National guidelines advocate the use of a standardised stroke identification tool

like FAST (Intercollegiate Stroke Working Party, 2016) due to its high sensitivity for stroke. Many ambulance trusts use FAST as the main, and sometimes only, inclusion criteria in their stroke pathways. FAST-ve was not individually strongly predictive enough in the development dataset to be included within STEAM nor was it considered in combination with other predictors as it did not point towards a specific non-stroke diagnosis. However, during STEAM refinement, FAST-ve was identified as being valuable for prediction of SM amongst patients that were being excluded from STEAM when the predictive threshold was raised from 1 to 2 points. This led to FAST-ve being included as an individual predictor variable as it worked well in conjunction with the other existing predictors. Being FAST-ve, especially in combination with other SM predictive characteristics, has face validity as FAST identifies the commonest stroke symptoms.

Blood glucose measurement is a common feature of existing pre-hospital stroke pathways so featured in STEAMv2 as a reminder to consider this common SM rather than creating duplication. There were nine patients with BM<3.5mmol/l in the refinement dataset, probably due to hypoglycaemia being identified and treated during pre-hospital assessment, so including BM within the SM tool would have had a negligible impact.

Consideration of whether to incorporate BM within STEAM and the alterations to the age criteria were examples of the how the focus group findings influenced the refinement process. STEAMv2 will be explored in a similar fashion in further focus groups which are reported in chapter 3.3.

The refinement of STEAM sought to maximise specificity and PPV and accepted that this would in all likelihood come at the expense of sensitivity. The various versions of STEAM exhibited differing combinations of these three performance measures, but the operational characteristic that most strongly influenced selection was the PPV. High predictive value in a small group of patients was accepted and understood in the focus groups which informed the refinement process. STEAMv2, despite not having the highest achievable PPV was considered to have the best balance of characteristics whilst retaining simplicity. Simplicity was also regarded as valuable by the focus groups and would help with training paramedics for the usability testing described in the next chapter and any future implementation.

2.2.11.1 Strengths and limitations

The refinement process followed clearly defined steps and utilised a larger dataset than the initial development of STEAM. The larger dataset generated more precise estimates, indicated by the narrower 95% confidence intervals, of the relative predictive strengths of the included variables.

The inclusion of data from three different acute trusts strengthens the generalisability of the results, although all three were within the North East. The data supplied by NTEES differed from the NHCT and NUTH data in terms of demographics and the percentage of patients with an assumed SM diagnoses. There may have also been differences in how diagnoses, stroke and SM, were made in the three trusts despite standard codes (ICD-10) being used e.g. from differences in the use of MRI, although the data in table 2.2.7 suggests that diagnostic practices were broadly similar.

There may be combinations of variables within the refinement dataset that were overlooked and there may be variables that would differentiate stroke and SM patients that were not collected in the dataset. Acknowledging these unknowns, STEAMv2 may be the best combination of variables that meets the aims of this thesis that is achievable with this imperfect dataset.

2.2.12 Conclusions

This chapter describes the refinement of the SM identification tool which resulted in STEAMv2. The iterative refinement process was based on a large pre-hospital dataset and informed by professional focus groups. STEAMv2 includes six characteristics which in combination identify a small number of SM patients with a high level of certainty. STEAMv2 achieved the stated aim of performing better than the original STEAM tool whilst retaining user simplicity.

2.2.13 Summary

The usability of a SM tool in clinical practice is reported in the next chapter along with initial views from paramedics about STEAMv2. The next chapter concludes part 2 of this thesis which has focussed on improving the initial STEAMv1 tool and collecting feedback from professional stakeholders about the development process and clinical usability of the tool. In

part 3 of the thesis STEAMv2 will be validated in a separate dataset, modelled to explore potential impact and discussed in a final phase of focus groups.

Chapter 2.3 Usability testing of the STEAM tool

2.3.1 Introduction

This is the second of three qualitative phases of the study. The first phase of qualitative work explored paramedics and hospital clinicians' views on the development of STEAM and was reported in chapter 2.1. The third phase reports paramedics and hospital clinicians' views on STEAMv2 and is reported in chapter 3.3.

2.3.2 Chapter aims

The primary aim of this chapter was to report prospective data on the acceptability and usability of the STEAM tool from the perspective of paramedics who applied the STEAM tool in practice. The secondary aim was to collect, analyse and report on qualitative data pertaining to paramedics' feedback on the mode, form and content of STEAM.

2.3.3 Methods

2.3.3.1 Design

A mixed methods design was used to address the aims of this phase of the study, with a generic qualitative approach (Cooper and Endacott, 2007; Griffiths and Mooney, 2011) due to the relative inexperience of the researcher and the multi-method nature of the wider project.

Volunteer paramedics were recruited and trained to use STEAM in their clinical practice over a period of up to 4 months as a service evaluation project. It was emphasised that this study was a data gathering exercise and STEAM was not to be used under any circumstances to change the clinical care of suspected stroke patients.

At the end of the data collection period quantitative data on the acceptability and usability of STEAM were collected from paramedics using a structured feedback form with 12 questions (appendix M). Semi-structured interviews with individual paramedics collected data on participants' views and experiences around applying STEAM in clinical practice. Prospective data on STEAM use in the pre-hospital setting were collected by evaluating Electronic Patient Care Records (EPCR) completed by participants regarding suspected stroke patients to establish what information pertinent to the STEAM tool was documented.

The original plan was to recruit 30 paramedics to prospectively test the STEAM tool. It was assumed this would allow 8-12 participants to be recruited for two focus groups consisting of 4-6 participants as informed by the recommendations of Barbour (Barbour, 2008) (p 60) and Pope and Mays (Pope and Mays, 2006) (p26). Due to smaller than expected numbers of participants, and the participants being paramedics who worked across a large area with differing shift patterns, it was difficult to arrange focus groups. Therefore, the participants were instead invited to individual semi-structured interviews.

The overall structure of the study is summarised in figure 2.3.1 below.

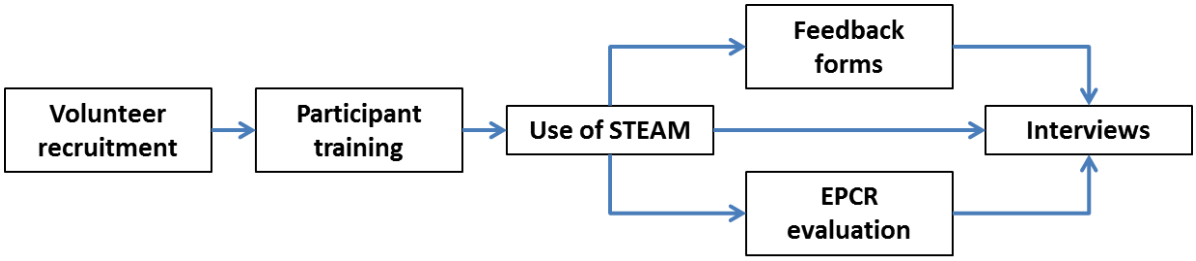


Figure 2.3.1 Overall structure of usability testing project

2.3.3.2 Participants

A volunteer sample of paramedics were recruited by advertising within NEAS using: mass email, circulation of information to staff by Emergency Care Clinical Managers, internal weekly bulletins and posts on social media (Twitter and Facebook). Paramedics were targeted as they are the main clinical decision makers in the pre-hospital setting. Paramedics within NEAS that were based at intervention stations in the PASTA study (Shaw *et al.*, 2016) were excluded to avoid contamination of either study.

2.3.3.3 Participant training

All volunteers were supplied with study information sheets and given the opportunity to ask any questions prior to participating. Once volunteers had provided their written consent to participate they were emailed the STEAM tool and an instruction sheet on how it should be applied, along with a STEAM aide memoire (see appendix N). All participants were offered face to face training if requested. Participants were asked to document STEAM characteristics and any use of STEAM on the EPCR so this could be evaluated.

2.3.3.4 Study timeframe

The study ran for four months from when the first participating paramedic started to use STEAM i.e. from 17/02/17 to 22/06/17. This time interval was selected based on allowing the participants at least one month to use STEAM in practice and the parallel work packages. At the end of the four months participants were informed that the study was completed, sent the feedback form and invited to participate in a semi-structured interview.

2.3.3.5 Data collection and analysis

The questions included within the feedback form were developed, with input from the supervisory team, around the usability and development of the STEAM tool and also covered some of the issues that emerged in the first focus groups (chapter 2.1). The feedback form was deliberately kept short (2 pages) with only 12 questions to encourage completion. Two questions required answers using a 5 point Likert scale and are reported using descriptive statistics. The remaining ten questions on the feedback form asked for freetext feedback and are reported using simple thematic analysis. Findings from the feedback forms were used to inform the semi-structured interviews.

The EPCR evaluation data was collected by NEAS informatics team executing a query using the participants NEAS ID number and searching for any cases during the study timeframe with a recorded impression of stroke. These cases were then examined for any documentation of STEAM characteristics or evidence of the application of STEAM. The data from the EPCR evaluation is presented using simple descriptive statistics. The evaluation results were used to inform the semi-structured interviews.

Participants were invited to take part in a semi-structured interview and offered a small incentive, in the form of a £10 Amazon voucher, as thanks for their time. Interviews were arranged at a time and place convenient for the participants. Informed written consent was gained at the start of each interview after participants had a chance to ask questions.

A topic guide was used for the interviews (see appendix O). The topic guide was developed with the support of the supervisory team after consideration of the survey data, and covered broad areas such as development of STEAM, application and barriers or facilitators to acceptability and usability. Due to the timing of the interviews, the revised version of the SM tool (STEAMv2) was added to the topic guide in order to gather some early opinions from

paramedics on the differences between STEAMv1 and STEAMv2. The topic guide was designed to help keep the interview focussed on issues of interest whilst allowing unexpected areas of discussion to arise.

Stimulus material (see appendix P) was used within the interviews. This consisted of the STEAMv1 tool, the results of the EPCR evaluation with reference to the presence of STEAMv1 characteristics, and the refined STEAMv2 tool. This was given to participants to act as reference material at appropriate points during the interview.

Digital audio recordings were made of the interviews and brief field notes were taken during the interviews and used by the researcher to ensure key points were covered and interesting points that arose were investigated without interrupting the flow of conversation. The audio recordings were transcribed verbatim by the researcher and anonymised for the purpose of analysis. The data analysis method for the semi-structured interviews was the same as used in chapter 2.1, thematic analysis using a five stage framework as described by Pope and Mays (Pope and Mays, 2006) (p72-74).

The findings from the interviews and the themes that emerged were discussed with the supervisory team. This debriefing, along with the use of direct participant quotes to illustrate themes, enhances the trustworthiness of the analysis.

2.3.3.6 Ethical approval

The three phases of qualitative work were granted research governance approvals as one project as reported in chapter 2.1.

An amendment was submitted to, and approved by, the HRA, NEAS and the Newcastle University Faculty of Medical Sciences ethics committee to include one-to-one semi-structured interviews for data collection.

2.3.4 Findings

Ten paramedics were trained and participated in this phase of the study. No paramedics requested face to face training. Participants used STEAM for a median of 89 days (IQR 55-111, range 43-125). The findings are based on four feedback forms, evaluation of 13 EPCRs from nine paramedics and three semi-structured interviews. The findings from the three data collection methods are presented separately. The feedback forms and semi-structured interviews represent 60% (n=6) of the 10 participants (one participant completed both a feedback form and participated in an interview). Participants are indicated by F1-4, Int2 for the feedback forms and P1-3, Int2 for the semi-structured interviews.

2.3.4.1 Feedback forms

The data collected from the feedback forms is summarised below. Anonymised illustrative quotes are used for some of the free-text questions.

Q1. What are your general thoughts on the mimic assessment tool?

All four participants thought STEAM was easy to use. One participant remarked on the low number of patients it was applicable to in practice.

Q2. How easy or difficult was it to include the mimic tool characteristics in your assessment?

On a five point scale (Very difficult, Difficult, Neutral, Easy, Very easy) 100% (n=4) of participants rated STEAM as very easy.

Q3. Did the mimic tool agree with your clinical decision making?

On a five point scale (Never, Rarely, Sometimes, Mostly, Always) 75% (n=3) of participants said always and 25% (n=1) said mostly.

Q4. What did you think about using the mimic tool in practice?

All four participants reported that STEAM was easy to apply in normal practice. Two participants remarked on the lack of stroke patients with any STEAM criteria they had seen and therefore their lack of opportunities to consider its use in practice. One participant suggested *"could the EPCR have a section for this like the sepsis recognition tool" F4, Int2*.

Q5. Are there any criteria within the tool that you think need changing?

Three participants said no to this question. The fourth participant questioned how patients with a history of migraine but who described a different headache to normal should be dealt with.

Q6. What format do you think the tool would be most useful in?

All four participants liked the aide memoires that were supplied. One participant suggested adding STEAM onto the EPCR.

Q7. What would be the best way to train paramedics to use this tool if it became part of normal practice?

All four participants felt STEAM was self-explanatory and little training beyond what was used in this study was actually needed, *"little training required, email or info leaflet" F2, Int2*.

Q8. When the tool indicated a patient may be a stroke mimic how would you have felt about not following your standard stroke protocol?

Three participants commented on the lack of opportunities to use STEAM. One participant said they would feel confident as long as STEAM fitted with national guidelines. A second participant said they would follow the normal stroke care protocol but with a *"confident handover that stroke mimic was a differential diagnosis" F1, Int2.*

Q9. How could you see the mimic tool fitting in with your local protocols?

Participants all felt STEAM could fit within local clinical protocols. One participant said *"The only thing that would need to be made clear is when the stroke bypass would not be implemented" F3, Int2.*

Q10. What do you think of the simplicity of the tool?

All four participants were positive about the simplicity of STEAM.

Q11. How would you feel about a more complex tool with different scores for different factors?

All four participants were happy with the idea of a more complex tool. One participant referenced the ABCD2 tool as an example of a more sophisticated tool already in use. One participant commented *"however due to the serious clinical nature of CVAs I feel it would be more beneficial to be more in depth, if we are using this to not use the stroke bypass" F3, Int2*

Q12. Is there anything else you think might be useful to the project going forward that we haven't asked about?

No further comments were made by the participants.

2.3.4.2 Evaluation of suspected stroke EPCRs

The NEAS informatics report identified 42 suspected stroke patients seen by nine participating paramedics within the study timeframe. During the usability testing NEAS changed its data collection system from the EPRF to the EPCR. Due to technical issues integrating the new EPCR system into practice there was no method of searching the EPCR database for a number of months. Using a manual process of searching calls attended by individual paramedics through the dispatch system the source data (EPCR) for 36% (n=15) of the suspected stroke patients were located. These EPCRs were examined for the presence, or documented absence, of STEAM characteristics recorded by participating paramedics.

Two suspected stroke patients were excluded due to low GCS; therefore the evaluation data is based on 13 EPCRs completed by participating paramedics and is reported in table 2.3.1

Table 2.3.1 STEAM characteristics recorded on the NEAS EPCR for suspected stroke patients during prospective testing

STEAM characteristics	**Recorded on EPCR (total=13)**	**%**
SBP	13	100
Temperature	12	92
HR	13	100
Seizures*	10	77
PMH Epilepsy	1	8
Age	13	100
Headache	8	62
PMH Migraine	1	8
STEAM or mimic tool	2	15

*The EPCR includes a Stroke/TIA section under 'Acute Medical Assessment'. Within this section convulsions are one or the characteristics that paramedics are requested to record. Therefore, this served as a prompt for paramedics to consider, and document, seizures.

2.3.4.3 Summary of feedback and EPCR evaluation

The feedback demonstrated that paramedics felt comfortable using STEAM but did not apply it very often. Participants thought that their training was sufficient and that adding STEAM onto the EPCR would be a good method of promoting consistent use. Although participants reported that they liked the simplicity of STEAM they were not averse to a more complex tool. The EPCR audit revealed that commonly completed observations, e.g. SBP, temperature, HR, and easily obtained information like age were all documented consistently. However, the presence or absence of headaches was less well documented and the presence or absence of epilepsy or migraine was rarely documented. The reasons for these differences, and the other findings of these two data collection methods, were explored in the semi-structured interviews.

2.3.4.4 Semi-structured Interviews

The findings from the three interviews are presented in a combined fashion due to the overlapping nature of the findings. Eleven themes emerged during data analysis. As STEAM had now been refined there was no attempt to combine this interview data with that obtained during the development phase. All the themes revolved around use of the STEAM. Three large categories: application, outcomes and thought processes emerged during the charting and mapping stage of analysis. These categories and themes are illustrated in figure 2.3.2. The themes are described below in more detail with illustrative anonymised quotes.

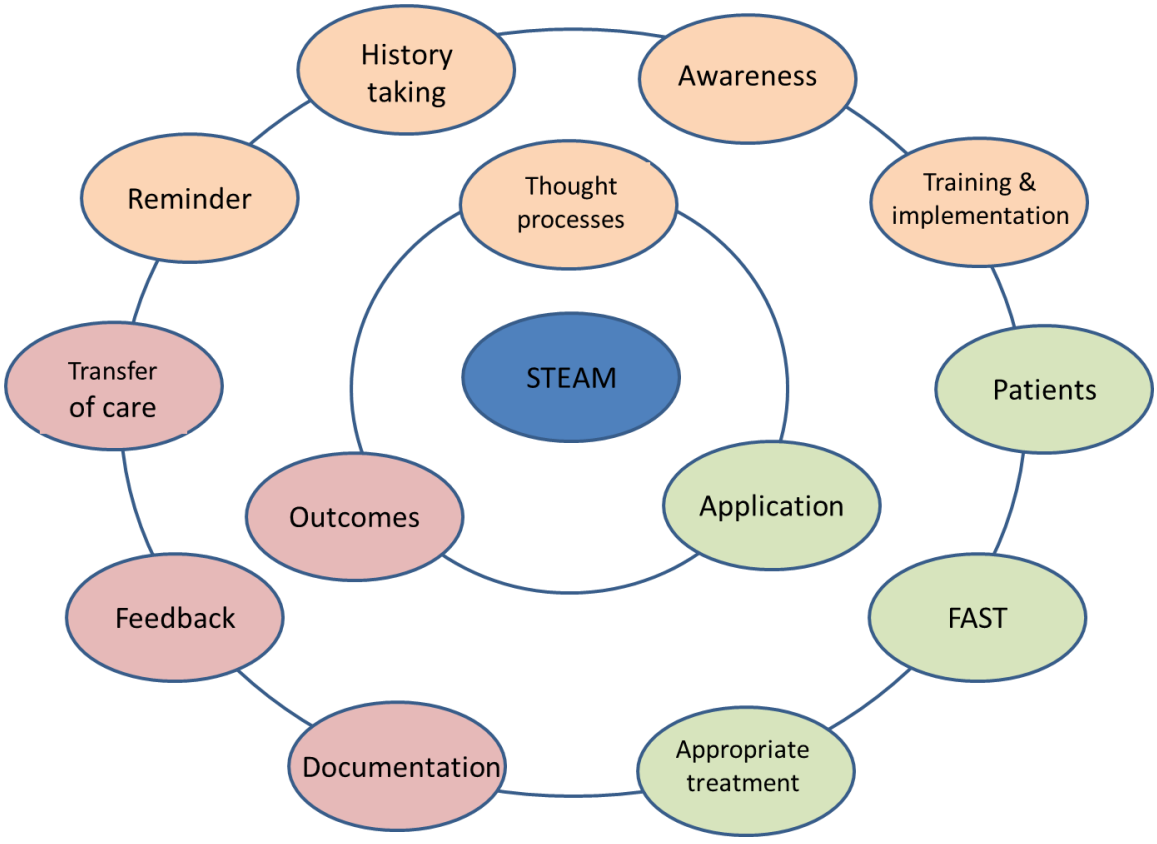


Figure 2.3.2 Map of themes emerging from interviews with paramedics with application (green), outcomes (red) and thought processes categories (orange)

The use of STEAM was at the centre of the discussions, although STEAMv2 was discussed briefly at the end of each interview. The three categories are arranged around the inner circle representing STEAM as the central theme with the other ten themes arranged around the outer circle:

- Thought processes (shown in orange in fig 2.3.2) which includes how the paramedic is trained on STEAM and how and with which patients they would decide to use it.

- Application (shown in green in fig 2.3.2) which includes when during patient assessment STEAM should be used and how it can interact with, and influence, the treatment of patients.
- Outcomes (shown in red in fig 2.3.2) which includes the outcome of applying STEAM in terms of transferring care to the hospital, feedback from the hospital to the paramedics and documentation.

2.3.4.5 The STEAM tool

All three participating paramedics thought that STEAM was simple and straightforward to use:

> *"Very simple in how it's set out and simple to use" P2, Int2*

In order to use the tool in practice, paramedics asserted that they would need to have confidence in the performance of the tool:

> *"I think people would have to have confidence in the tool, that it was doing what it says it's going to do" P1, Int2*

The age criterion in STEAM was discussed. One participant linked this to their training where stroke was associated with older age, and another participant questioned the inclusion of age as a criterion:

> *"Just because you're under 40 I mean doesn't rule you out does it, so, I've been to patients younger than 40 who have had a stroke." P1, Int2*

This same participant did acknowledge why they remembered these patients:

> *"Cause they're unusual" P1, Int2*

The question of putting the tool onto the EPCR to make it easier to access and record was raised by two of the paramedics:

> *"Is the plan to have this as part of the EPRF (*EPCR*) so you can have like the sepsis, in the stroke element where you do all your checks" P3, Int2*

In summary participants reported that STEAM was acceptable for use in the pre-hospital setting. There were no suggestions of changes to the variables in STEAM, but suggestions

around the format and presentation of the tool such as making it part of an algorithm or flowchart for ease of understanding were made.

Participants were introduced to STEAMv2 in order to gather their views on the revised tool. STEAMv2 was presented in isolation and participants commented that it would be better if it was presented in a more user friendly format such as an algorithm or flowchart:

> *"You could lay it out differently so it's a bit more, you know, what's the word, just a bit more friendly I suppose" P1, Int2*

The refinements were accepted by the participants who understood the reasons for the changes. Participants thought the inclusion of BM improved the tool and that STEAMv2 was still simple and straightforward despite the addition of another variable and the need to score 2 points:

> *"It's very simplistic in the way it's laid out so perfect, I think it's very straightforward to use." P2, Int2*

2.3.4.6 Thought processes

The following four themes have been grouped together as they all involve the thought processes behind 'how and when' the paramedics would use STEAM. This includes participant's views on when STEAM would be thought relevant, how SMs were something they had previously given very little attention, and their views on how paramedics could be trained on STEAM.

2.3.4.7 History taking

All three participants described the importance of a good patient history as part of deciding whether a patient was a stroke or a SM:

> *"It's the history taking that's got to be absolutely specific and accurate" P3, Int2*

The difficulties in establishing a clear history for some patients were also recognised and how third parties were sometimes the only source of pertinent information:

> *"You'd be getting history from a third party, so you would still, you would treat a dementia patient with a bit more caution though wouldn't you because they can't, sort of interact with and confirm or deny something" P1, Int2*

One participant described their assessment process in three stages: first rule out any immediate threats to life; second take observations and a good history; third make a decision on what to do with the patient. They saw the history taking as being key to informing the decisions that were made. They also thought underpinning knowledge and awareness of differential diagnoses was important in terms of guiding the history taking. Participants thought that STEAM would help ensure relevant questions were asked during the history taking and that the documentation of the history taking could be improved.

2.3.4.8 Awareness

Two participants reported a lack of awareness of SM prior to being involved in this research:

> *"Till I started I don't think I had been aware of such a condition or other causes" P2, Int2*

These same two participants both reported that their involvement in this research was due to personal interest in stroke as a condition:

> *"It's only been my personal interest in strokes, as you know, that has made me develop my sort of learning a lot more" P3, Int2*

Awareness of signs, symptoms and risk factors for stroke or SM is important as this can guide the history taking and patient assessment, which in turn determines the actions taken by the paramedic. Participants said they were unaware that seizures could lead to stroke-like symptoms in some patients:

> *"In all honesty before this I've never put a stroke in an epileptic" P3, Int2*

One participant reported that they mentored student paramedics who they felt had limited knowledge about stroke, TIA or SM. This links in to the training that paramedics receive around stroke and emphasises the potential value of STEAM in raising awareness of stroke in paramedics.

2.3.4.9 Training and implementation

There was a lot of discussion within all three interviews around how paramedics could be trained to use a tool like STEAM and how it could be integrated into their decision making

process. Explaining to people why they should use STEAM was felt to be vital to successful implementation:

> *"I think a lot of people can be convinced to do something or can be more inclined to do something if they know why they're doing it" P1, Int2*

There were numerous suggestions for how to best train staff to use STEAM including the use of social media, podcasts, introducing SM during pre-registration education, using Emergency Clinical Care Managers (paramedic team leaders in NEAS) to train other staff as well as using the annual mandatory training days that all NEAS staff must attend. One interesting observation that was made was about how STEAM would be presented to paramedics and whether it was seen as optional or not:

> *"If you give people the option to use it or not they won't use it" P1, Int2*

This point was reflected in discussions around how organisational support would be vital to give paramedics the confidence to use a new tool like STEAM. One way that STEAM could be endorsed by the organisation would be to mandate its use by including it in the stroke care bundle (documentation of FAST status, blood pressure and blood sugar):

> *"I think putting it into the care bundle would be, it's almost mandating it, isn't it" P1, Int2*

2.3.4.10 Reminder

STEAM was seen as a good way for people to check they had asked relevant questions during their patient assessment, with the aide memoire considered to be a useful checklist. This represents paramedics using STEAM at the end of the decision making process as opposed to the history taking theme which referred to paramedics using STEAM earlier in the assessment process:

> *"I think I would use it as a checklist, after, I think, rather than as a prompt" P1, Int2*

All three participants said they carried the aide memoire around and referred to it when they had a patient who they thought may be suitable. Participants suggested using the EPCR to automatically trigger people to consider STEAM when stroke symptoms were documented. One participant explained how completing the various sections on the EPCR served to reassure them that they had documented a thorough assessment:

"I've ticked all these boxes and I kind of know that this is where I'm going and great, and it just gives you that little bit of security that you've seen it on black and white" P2, Int2

This use of the EPCR links into the documentation theme in the outcomes section.

2.3.4.11 Application

The following themes were grouped together as they converged on how STEAM could be applied in practice. This includes how STEAM interacts with FAST, patients where participants thought STEAM would be useful and how STEAM could influence decision making about appropriate treatment for suspected stroke or SM patients.

2.3.4.12 FAST

One participant expressed how the FAST test was seen as *"very basic" P3, Int2* and that STEAM gave paramedics an opportunity to develop their stroke recognition beyond FAST. Another participant expressed concern about how STEAM would interact with FAST:

"That might cloud the issue a little bit if someone's FAST positive" P1, Int2

Participants referred to practice at local hospitals where some EDs would not expect to see FAST positive patients. An example was given where the paramedic tried to admit a patient to a local stroke unit based on a positive FAST test, but the stroke unit thought the patient should be seen at ED and the ED thought the patient should be seen on the stroke unit. This shows the importance of the FAST test in pre-hospital stroke recognition and how pathways are organised around it. If STEAM were to be implemented, how the results of STEAM would interact with the results of FAST would need to be very clearly described.

2.3.4.13 Patients

All three participants reported being unable to use STEAM as often as they anticipated:

"Within the length of the trial I don't think I've had anybody who's actually met any of the criteria that are on there" P2, Int2

Whether this lack of opportunities was due to the short length of the usability study, the low number of suspected stroke patients encountered or whether paramedics automatically

decided that the majority of patients were not suitable for STEAM would be areas for future research.

In contrast to the previous point, there was recognition that STEAM was applicable to most suspected stroke patients. However, it was acknowledged that in certain groups of patients, such as those with cognitive or communication difficulties, it would be more challenging to apply STEAM. There was also acknowledgment that geographical factors, in terms of distance to hospital for rural patients, and temporal factors, primarily whether the patient was in the thrombolysis treatment window, came into play when assessing stroke patients:

> *"If it is going to be a stroke and you have caught it at a particular time then you want to be able to act on it in the same way that you want to be able to do the right thing by a stroke mimic" P3, Int2*

2.3.4.14 Appropriate treatment

Participants recognised that appropriate treatment for SM patients may not be admission to a stroke unit and that diverting SM patients to other pathways could free up specialist stroke resources:

> *"If we're being given more informed information, that's going to benefit those people and free up the stroke departments" P3, Int2*

There was recognition of the need for a high level of certainty in the SM diagnosis which linked to the history taking theme. Paramedics felt accountable for their treatment of suspected stroke patients and wanted to provide the best possible care. A thorough history would need to be taken to ensure that variables that could influence the decision making had all been considered:

> *"There's potential dangers attached too, it's being absolutely certain that you're not going to miss out on something that's quite crucial" P3, Int2*

Opinions differed as to what participants felt was appropriate treatment for a SM:

> *"If the patient was showing classic stroke symptoms I would still err down that pathway, stroke pathway, but I would be mindful of the fact that it might be a mimic but I would still treat for the worst case scenario" P2, Int2*

*"We can treat those patients (*SM*) appropriately which may not be transporting them to a stroke unit or to a major hospital if they need to be more appropriately treated locally" P1, Int2*

Participants agreed that transportation to hospital was still the appropriate treatment for SM patients, which links to the hospital theme, as these patients would have an underlying (potentially serious) issue that would need investigation and treatment:

"You're recognising a stroke mimic and you're getting that seen to and whatever's wrong with them treated" P3, Int2

2.3.4.15 Outcomes

The final grouping describes themes relating to the impact and outcome of applying STEAM. This includes: how STEAM would be received by hospital staff and departments; feedback that paramedics receive on stroke patients; and how suspected stroke patient encounters are documented.

2.3.4.16 Transfer of care

The interaction between paramedics and the hospital was a topic discussed by all three participants. The influence that the hospitals reception would have on paramedic use of STEAM was raised:

"People would need to have confidence that hospitals were going to be accepting of this being a recognised method of filtering patients" P1, Int2

"As long as the departments that are receiving are understanding why you're coming in, even though the presenting complaint was possible stroke" P3, Int2

This linked into the need for the pathways to hospital to be clear with both paramedics and hospital staff having a good understanding of the tool and the implications of its use. The differing departments that patients could be admitted to, which was highlighted in the FAST theme, was a prominent issue:

"If you're going to a different department but in the same hospital, it's not so much of an issue, but if you're going to a completely different site, then that's a big issue" P1, Int2

This difference in potential destinations links closely to the appropriate treatment theme as paramedics recognised that not every hospital has a stroke unit and getting the right patient to the right hospital was a key part of their role.

2.3.4.17 Feedback

The lack of feedback paramedics receive on suspected stroke patients was raised in two interviews as a potential influence upon how well STEAM would be adopted in practice. When feedback was received it was informal and only because the paramedic actively sought it out from hospital staff. The benefits of feedback regarding the accuracy of the pre-hospital diagnosis for suspected stroke patients (and other patients) were described by one participant:

> *"You want to know that you're making the right decisions about all your patients and yet unless you ask or you mess up majorly you don't get to hear any of that feedback so how are you supposed to learn?" P2, Int2*

One participant reported receiving feedback on suspected stroke patients, but only if they took them directly to the CT scanner. This was an example of the differing practices of departments within a hospital and how feedback can be linked to, and influenced by, the practices of the individual hospital or department. As STEAM would be a new intervention then feedback would be important to reassure paramedics that the right decisions had been taken or to identify examples where the wrong decisions had been made so lessons could be learnt and care could be improved.

2.3.4.18 Documentation

The place of STEAM during completion of clinical record documentation by the paramedics was a theme that emerged during discussions of the EPCR evaluation. One issue raised with extracting data from the EPCR was assuming something hadn't happened because it wasn't written down:

> *"If they haven't filled it in, is it because they weren't aware or is it because the patient didn't show any of those things." P2, Int2*

This led into a discussion around how paramedics decide what needs to be documented and how some results and findings are recorded without explaining the decision making or process by which they were reached:

> *"I think in terms of documenting it, that might be that people maybe thought like because I'm using it I don't need to document it, almost as such like you would document a GCS but you wouldn't document that you were using the GCS method of assessing someone's consciousness level" P1, Int2*

This links into the awareness and training themes. Paramedics need to know which information is relevant in order to target questioning and patient assessment, and also in order to record appropriate information.

Participants described how documenting the patient encounter could act as a trigger to consider use of STEAM:

> *"It was probably only something that I thought about in depth once I was doing my write up" P2, Int2*

Discussing the write up of the patient encounter led to how documentation was needed to support and justify clinical decisions, which is especially important when a tool like STEAM may indicate alternatives to current standard practice:

> *"Your documentation, well, it's justifying your reasons as to why you've done that" P2, Int2*

This could be an example of defensive practice where a recognised tool or assessment would be used to defend the decision which may be later challenged.

2.3.5 Discussion

This chapter reports the views and experiences of paramedics who were trained on STEAM and applied it in practice. The aim was to explore acceptability and usability and how STEAM could fit into clinical care when it was applied during the assessment of real patients.

The interviews allowed the participating paramedics' experiences to be recorded, as well as allowing the EPCR evaluation results and the findings from the feedback forms to be explored in more depth within a meaningful context.

The EPCR evaluation showed that basic observations were consistently documented whereas aspects of the patient's PMH, such as history of migraine or epilepsy, were rarely recorded. The lack of documentation of PMH is supported by previous work which showed that paramedics documented PMH less frequently than hospitals (Rudd *et al.*, 2016b). The reasons for this were explored during the interviews and included paramedic perceptions about what was relevant information to document during routine assessment of suspected stroke.

The feedback forms and interviews showed that the participants were positive about STEAM and considered it to be usable in the pre-hospital setting. They understood why SM identification was important and the potential benefits from routine assessment for this purpose. The training, although short, was considered sufficient which overcomes the issue of arranging face to face training, as this is difficult with a geographically widespread workforce (Ankolekar *et al.*, 2014).

Participants thought STEAM was simple, easy to use, fitted into their normal clinical assessments and could improve the transfer of care to the hospital. Use of a standardised tool to transfer information from the pre-hospital to the hospital setting has been shown to improve efficiency of information handover (Iedema *et al.*, 2012). Feedback from the hospitals about the paramedics' stroke diagnosis was infrequent but perceived as beneficial which mirrors previous findings (Hodell *et al.*, 2016). Participants were also aware of the risks inherent in missing a true stroke patient based on application of STEAM and wanted STEAM to be as specific as possible if it was to be used in practice.

Previous qualitative analysis of paramedic's views on pre-hospital stroke research (Ankolekar *et al.*, 2014) revealed that simplicity was valued by paramedics and that individual

paramedics encountered few suitable stroke patients, both of these findings were replicated in this work. The low rate of use was not unexpected given the number of participants, the duration of the testing and the small number of SM cases where STEAM would be triggered. Individual paramedics see relatively few strokes and confidence with a study intervention can come from repeated use (Ankolekar *et al.*, 2014). This would need to be considered if STEAM were to be introduced as paramedics may forget or not complete items appropriately if it is rarely used in practice. Building STEAM into a bundle of care, a pathway or using a reminder like the EPCR may help embed it within practice and overcome the barrier of infrequent use. Bundles of care have been developed for stroke, and other conditions, and shown to standardise the collection and reporting of data and lead to improvements in care (Siriwardena *et al.*, 2014).

Various aspects of paramedic's interactions with receiving hospitals were raised in the interviews. The influence of local pathways including which units would take stroke patients was discussed, which gave some context for how STEAM could change current practice. Paramedics have placed high importance on clear patient benefit and reported seeing their role as enabling access to the best treatment (Burges Watson *et al.*, 2012) especially through getting the right patient to the right hospital. When all suspected stroke patients go to a single location the paramedics' opinion has lower risk attached, but if a SM tool and redirection pathway were introduced then the risk of making the wrong decision has greater consequences.

Discussing the interaction with receiving hospitals revealed a desire for feedback regarding transported suspected stroke patients. The lack of feedback has previously been reported as a concern for paramedics as it is seen as necessary to improve services (Oostema *et al.*, 2016). The introduction of a new assessment like STEAM would benefit from an established feedback system to encourage consistent completion and ongoing learning about SM presentations.

Paramedics appeared to be comfortable with the idea of taking SM patients to ED rather than a stroke unit. SM presentations include a wide range of conditions, some of which are potentially life threatening or life changing similar to a stroke and some of which are less immediately concerning. The comment in the appropriate treatment theme about erring on the side of caution gives an insight into the mind-set of some paramedics who will always

treat for the worst case scenario and take the patient to where they perceive they will get the highest level of care. This mind-set could be driven by historic practices of taking every patient to hospital and perceptions of which hospitals provide the best care for a patient, but there may also be issues around accountability and what is perceived as the least risky option for the paramedic and the patient. This comment also highlights the difficulties clinicians face when trying to apply a decision tool derived from a population level dataset to an individual patient. Whether STEAM is perceived as a checklist, part of an algorithm with pre-determined actions or whether it is perceived as supporting autonomous decision making will depend on the paramedic in question and their view on how the profession should practice.

2.3.5.1 Implications for overall project and future work

The themes described in this chapter build upon those described in the initial focus groups (chapter 2.1). There are areas of overlap between themes including the actions triggered by STEAM, the decision making by the paramedics and how STEAM could be implemented across pre-hospital and acute trusts. Despite the low usage of STEAM the findings from this phase are useful for informing the development of STEAM to enhance its acceptability and usability. Key points that emerged were:

- The age criterion was an area of concern.
- The omission of BM was addressed in the criteria for STEAMv2.
- The actions triggered by STEAM would need to be made clear during implementation.

2.3.5.2 Strengths and limitations

The findings reported in this chapter were largely consistent with the views expressed by paramedics in the national survey (chapter 1.3) and in the previous focus groups (chapter 2.1) which reinforces the credibility of the findings.

The small number of participants, and the lack of data from 40% of the participants, are limitations of this study. Technical issues at NEAS led to an inability to access a large number of EPCRs which limited the data available for the documentation evaluation. The non-responders to the interview invitation may have had different experiences and views to those reported which would be a source of responder bias. The participants who did

respond agreed on most major topics regarding the acceptability and usability of STEAM. The small number of interviews, and the particular interest in stroke reported by two of the interview participants, means that these findings may not be representative of the wider paramedic population. As the aim of this work was to inform the development and future application of the STEAM tool, this is probably a lesser concern than might be the case for other studies, such as a process evaluation of a new intervention.

Reflecting on the interviews forced me to consider whether my position as the researcher conducting the interviews may have influenced the findings. I was known to the participants, which is largely unavoidable in a small service like NEAS. I had no managerial responsibilities over any of the participants and did not work directly with them. However, it is still possible that the participants chose to assist and provide specific views because of pre-existing associations.

2.3.6 Conclusions

Paramedics who applied STEAM during the assessment of real patients found it easy to use. Participants liked the simplicity of STEAM but were open to a more complex tool and considered that STEAMv2 was acceptable. Paramedics reported a general lack of awareness or knowledge of SM which highlights the need for effective training on STEAM to support implementation in practice. There were no suggestions on changes to STEAM although the inclusion of a young age cut-off was questioned again. Clarifying the actions that application of STEAM could lead to, and how this could affect paramedics' interactions with receiving hospitals, were key issues raised by participants.

2.3.7 Summary

The findings reported here build upon the stakeholder work reported in chapters 1.3 and 2.1 and support the development of STEAM and the refinements made with STEAMv2. There were useful suggestions around how to implement STEAM in practice. No major issues with STEAM or STEAMv2 were raised by participants, although a positive responder bias should be considered.

Chapter 3.0 Summary of parts 1 and 2 and overview of part 3

3.0.1 Introduction

This brief chapter will recap parts 1 and 2 of the thesis and give a short overview of part 3. Figure 1.0.2 from chapter 1.0 is repeated below to illustrate the overall research process.

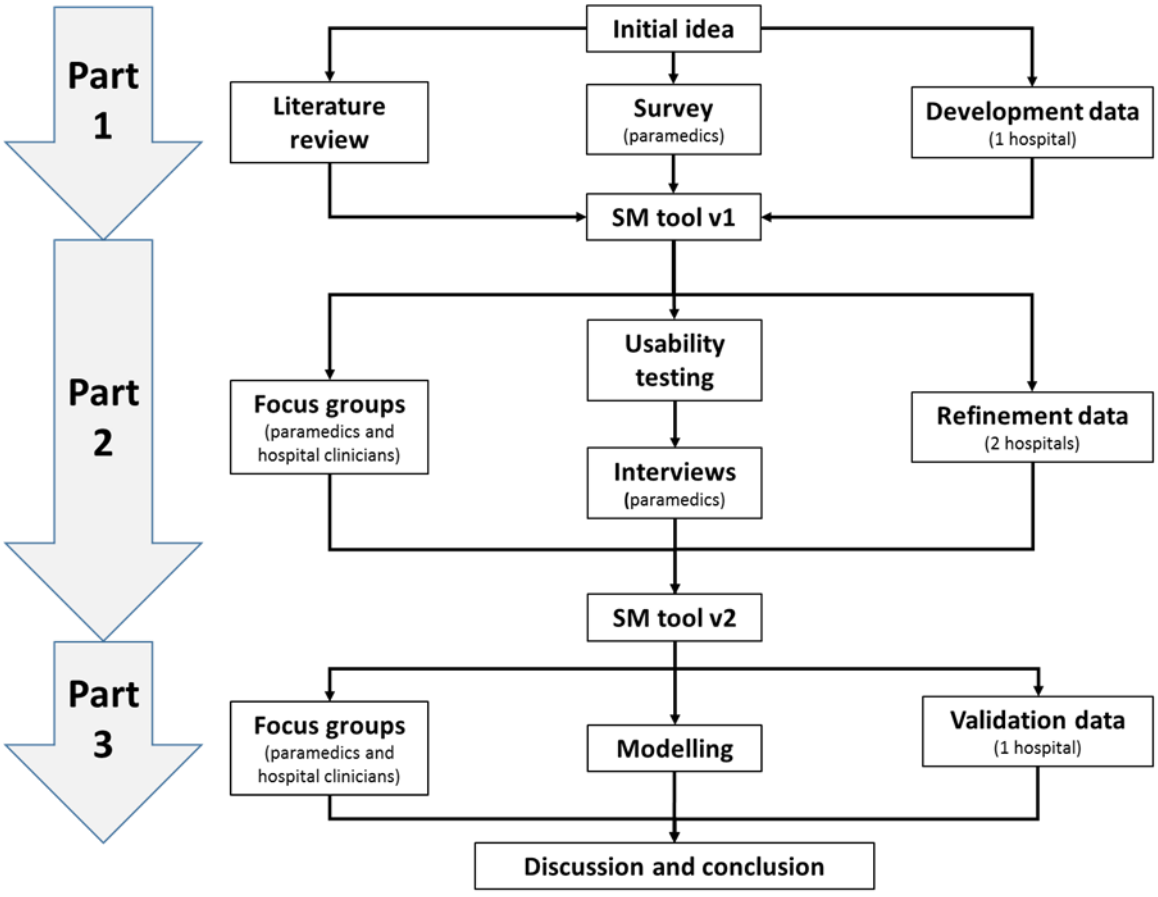


Figure 1.0.2 Flowchart with overview of pre-hospital SM project

3.0.2 Summary of part 1

Part 1 described the background to pre-hospital and emergency stroke care. The systematic review summarised the frequency, underlying aetiology and common characteristics of SM and identified that SM were commonly encountered in the pre-hospital setting. The systematic review, the stroke focussed survey of UK paramedics and the creation of a linked dataset describing suspected stroke patients transported to NHCT by NEAS led to the development of the STEAM tool.

3.0.3 Summary of part 2

Part 2 reported focus groups and interviews with paramedics and hospital clinicians which allowed their views around SM and the development, strengths and weaknesses of STEAM to be included within the development process. Part 2 described the refinement of STEAM into STEAMv2 based on the findings of the focus groups and expansion of the dataset from 1,650 to 3,797 suspected stroke patients which improved the generalisability and the power of the predictive variables.

3.0.4 Overview of part 3

Part 3 includes the validation of STEAMv2 using a new dataset (n=1,848 suspected stroke patients) from a fourth acute trust which is reported in chapter 3.1. Chapter 3.2 employs a basic modelling approach to consider what high level impact STEAMv2 could have if it was introduced into clinical practice. Part 3 concludes with paramedic and clinician focus groups across two regions, the North East and the North West, to report professional stakeholder views on STEAMv2.

Chapter 3.1 Validation of the STEAMv2 tool

3.1.1 Introduction

STEAMv2 was developed and refined using data on suspected stroke patients transported by NEAS to three acute hospital trusts (NHCT, NUTH, NTEES). This chapter describes the validation of STEAMv2 which is the next stage in the development process. Validation involves testing the tool on new patients i.e. a dataset from a different source to the one used during development. It is important to validate a new tool in order to demonstrate that it performs as expected across other settings before it can be considered for widespread clinical use (Stiell, 1996; Altman *et al.*, 2009).

Three methods of validating a tool have been identified: internal, temporal and external (Altman *et al.*, 2009). Internal validation involves splitting a single dataset into two parts, a training set and a validation set. Temporal validation involves data from the same location but from a separate time period. External validation requires data from a different location to the original development dataset. In order to externally validate STEAMv2 data were collected from a fourth hospital trust and STEAMv2 was tested in this new dataset.

3.1.2 Chapter aim and objectives

The aim of this chapter is to describe external validation of the STEAMv2 tool.

This objectives are:

- Describe an external validation dataset of suspected stroke patients.
- Determine the performance of STEAMv2 in the validation dataset.

3.1.3 Methods

The validation dataset was created using the same methods as the development (chapter 1.4) and refinement (chapter 2.2) datasets. The method is summarised below:

- Suspected stroke patients transported by NEAS were identified.
- Data on variables relevant to stroke or SM diagnoses were collected from NEAS records.
- NEAS suspected stroke patients were linked with hospital SSNAP and HES records to establish discharge diagnoses.

3.1.3.1 Setting

Data for the external validation were collected from County Durham and Darlington NHS Foundation Trust (CDDFT) which includes two acute hospitals in the North East. University Hospital of North Durham (UHND) has a stroke unit and receives all stroke patients from the CDDFT catchment area. Darlington Memorial Hospital (DMH) is the second CDDFT acute hospital but does not routinely accept stroke patients. CDDFT provides care to around 650,000 people in County Durham and the surrounding area. CDDFT admitted 691 confirmed stroke patients in 2016/17. CDDFT consistently performs well in the SSNAP audit in criteria relevant to this work such as case ascertainment where it scored 80-90%+ from 2014 onwards (RCP, 2017b).

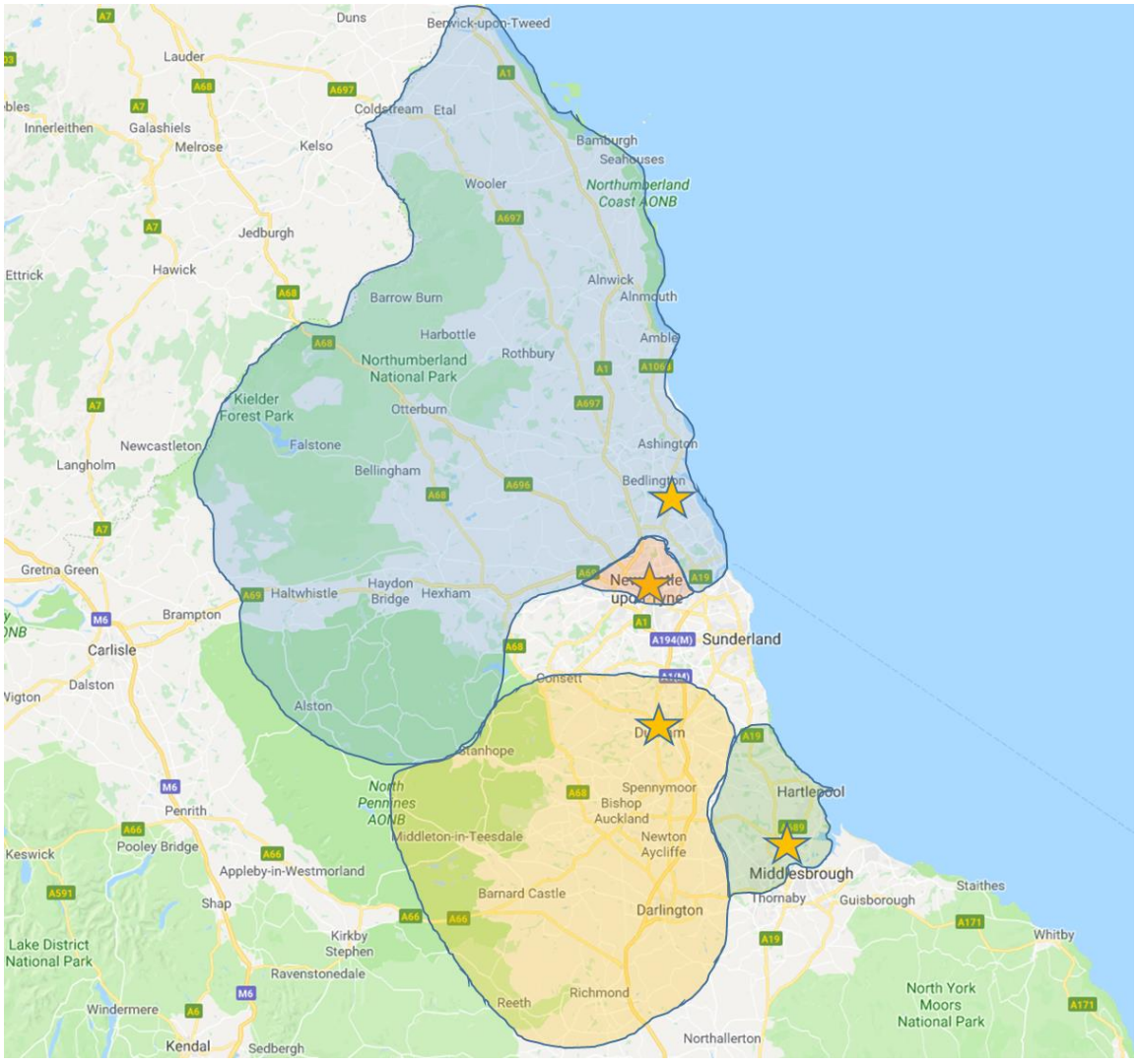


Figure 3.1.1 Map of the North East showing approximate catchment areas of all included hospital trusts. CDDFT is the lower left trust

Data were collected over the same period as the development and refinement cohorts.

3.1.3.2 Data analysis

Extraction, linkage and analysis of all data followed the same processes described in chapter 1.4. All data were extracted into Excel and imported into SPSS for analysis.

3.1.3.3 Approvals

Local approvals were secured from NEAS and CDDFT for data sharing.

3.1.4 Results

3.1.4.1 The validation dataset

There were 1,848 suspected stroke patients, including 605 (33%) SM, transported by NEAS to CDDFT hospitals within the study timeframe.

3.1.4.2 Patient Selection

The process of identifying suspected stroke patients transported by NEAS to CDDFT hospitals is shown in figure 3.1.2.

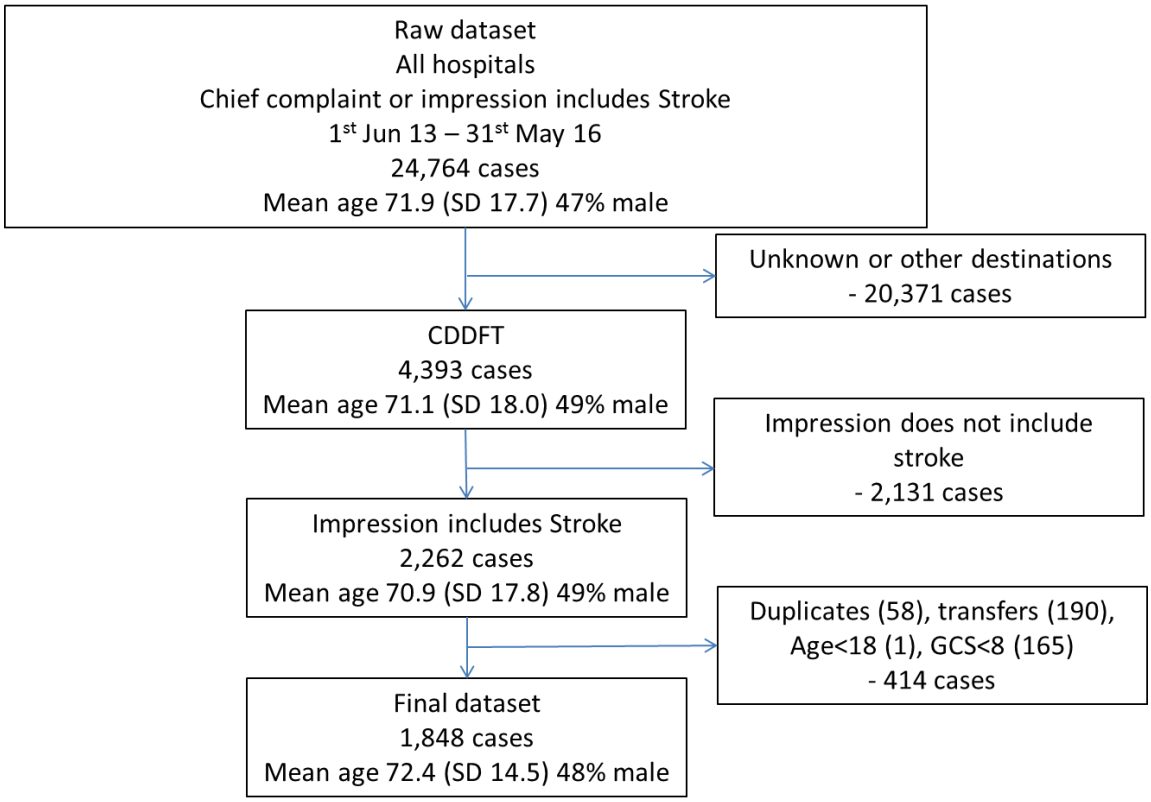


Figure 3.1.2 Identification of NEAS suspected stroke patients transported to CDDFT

3.1.4.3 Patient discharge diagnoses

From the total cohort of 1,848 suspected stroke patients 915 (50%) were identified as stroke patients using SSNAP. The remaining 933 suspected stroke patients who were not positively matched with the SSNAP data were searched for using the CDDFT electronic record system (HES).

- 156 patients were identified as TIA (ICD-10 codes G458 and G459) based on CDDFT HES records.
- 172 patients were identified as stroke based on CDDFT HES records including diagnostic codes I61, I63 and I64.
- 414 patients had a SM ICD-10 diagnosis.
- 191 patients were unable to be linked with either SSNAP or HES. These patients were all assumed to be SM.

Combining these figures results in 1,243 (67%) stroke patients and 605 (33%) SM patients.

3.1.4.4 CDDFT assumed SM patients

SM patients were identified (n=605) by either confirmed non-stroke diagnosis (n=414, 68%, including any ICD-10 code other than I61, I63, I64 or TIA codes G458 and 459) in CDDFT HES system or assumed (n=191, 32%) based on inability to match with either SSNAP or HES.

The patients assumed to be SM were compared with the patients with a confirmed SM diagnosis.

Table 3.1.1 Comparison of CDDFT patients with confirmed SM diagnoses versus assumed SM diagnoses

Diagnosis	Age (mean, SD)	Gender (% Male)
Confirmed (n=414)	67.8 (16.9)	45
Assumed (n=191)	71.2 (17.1)	47

The two groups of SM patients were significantly different in age (independent samples t-test, p=0.022) but not significantly different in gender (chi square test, p=0.615).

3.1.4.5 SM diagnoses

One hundred and forty different ICD-10 diagnostic codes were recorded for the 414 patients with a confirmed SM diagnosis. The ICD-10 based SM diagnoses are displayed in table 3.1.2.

Table 3.1.2 Most frequent ICD-10 diagnoses recorded for CDDFT SM patients

ICD-10 Code	ICD-10 description	Number (%) of patients
R568	Convulsions, not elsewhere classified	34 (8%)
G819	Hemiplegia, unspecified	25 (6%)
R298	Other symptoms and signs involving the nervous and musculoskeletal systems	25 (6%)
R55X	Syncope and collapse	24 (6%)
G510	Bell's palsy	20 (5%)
N390	Urinary tract infection, site not specified	17 (4%)
G439	Migraine, unspecified	15 (4%)
R478	Other speech disturbances	12 (3%)
R51X	Headache	11 (3%)
R410	Disorientation, unspecified	9 (2%)
G409	Epilepsy, unspecified	8 (2%)
J181	Lobar pneumonia, unspecified organism	8 (2%)
R268	Other abnormalities of gait and mobility	7 (2%)
R470	Dysphasia and aphasia	6 (1%)
G431	Migraine with aura	5 (1%)
I219	Acute myocardial infarction, unspecified	5 (1%)
C793	Secondary malignant neoplasm of brain and cerebral meninges	4 (1%)
F059	Delirium due to known physiological condition	4 (1%)
G403	Generalized idiopathic epilepsy and epileptic syndromes	4 (1%)
I609	Nontraumatic subarachnoid hemorrhage, unspecified	4 (1%)
I620	Nontraumatic subdural hemorrhage	4 (1%)
I629	Nontraumatic intracranial hemorrhage, unspecified	4 (1%)

Table 3.1.2 Most frequent ICD-10 diagnoses recorded for CDDFT SM patients cont.		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
J22X	Unspecified acute lower respiratory infection	4 (1%)
R296	Repeated falls	4 (1%)
Other	Other conditions with less than 1% (n=4) prevalence	151 (36%)

The ICD-10 codes were summarised using CCS codes as used in earlier chapters. The most frequent SM diagnoses represented using level 2 CCS codes are shown in table 3.1.3.

Table 3.1.3 CDDFT SM diagnoses displayed using level 2 CCS codes		
CCS level 2 code	**CCS description**	**Number (%) of patients**
6.9	Other nervous system disorders	55 (13%)
6.4	Epilepsy; convulsions	52 (13%)
6.5	Headache; including migraine	34 (8%)
13.8	Other connective tissue disease	30 (7%)
17.1	Symptoms; signs; and ill-defined conditions	29 (7%)
6.3	Paralysis	28 (7%)
10.1	Diseases of the urinary system	20 (5%)
7.3	Cerebrovascular disease	17 (4%)
7.2	Diseases of the heart	15 (4%)
8.1	Respiratory infections	13 (3%)
Unknown	Unknown	9 (2%)
5.4	Delirium dementia and amnestic and other cognitive disorders	7 (2%)
6.8	Ear conditions	6 (1%)
7.4	Diseases of arteries; arterioles; and capillaries	6 (1%)
16.2	Fractures	6 (1%)
5.5	Developmental disorders [654]	5 (1%)
6.2	Hereditary and degenerative nervous system conditions	5 (1%)

Table 3.1.3 CDDFT SM diagnoses displayed using level 2 CCS codes cont.		
CCS level 2 code	**CCS description**	**Number (%) of patients**
2.12	Secondary malignancies [42.]	4 (1%)
2.3	Cancer of bronchus; lung	4 (1%)
6.1	Central nervous system infection	4 (1%)
8.8	Other lower respiratory disease	4 (1%)
16.4	Intracranial injury	4 (1%)
Other	Other conditions with less than 1% (n=4) prevalence	57 (14%)

The CCS codes were combined into level 1 CCS codes to show broader clinical groupings as shown in table 3.1.4.

Table 3.1.4 CDDFT SM diagnoses displayed using level 1 CCS codes		
CCS1 code	**CCS code description**	**Number (%) of patients**
1	Infectious and parasitic diseases	4 (1%)
2	Neoplasms	15 (4%)
3	Endocrine; nutritional; and metabolic diseases and immunity disorders	9 (2%)
5	Mental Illness	21 (5%)
6	Diseases of the nervous system and sense organs	187 (45%)
7	Diseases of the circulatory system	39 (9%)
8	Diseases of the respiratory system	23 (6%)
9	Diseases of the digestive system	3 (1%)
10	Diseases of the genitourinary system	22 (5%)
12	Diseases of the skin and subcutaneous tissue	1 (<1%)
13	Diseases of the musculoskeletal system and connective tissue	35 (8%)
16	Injury and poisoning	17 (4%)

Table 3.1.4 CDDFT SM diagnoses displayed using level 1 CCS codes cont.		
CCS1 code	**CCS code description**	**Number (%) of patients**
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	29 (7%)
18	Residual codes; unclassified; all E codes [259. and 260.]	9 (2%)

The CDDFT SM diagnoses are graphically displayed in figure 3.1.3 with figure 1.2.3 from the literature review repeated below for comparison.

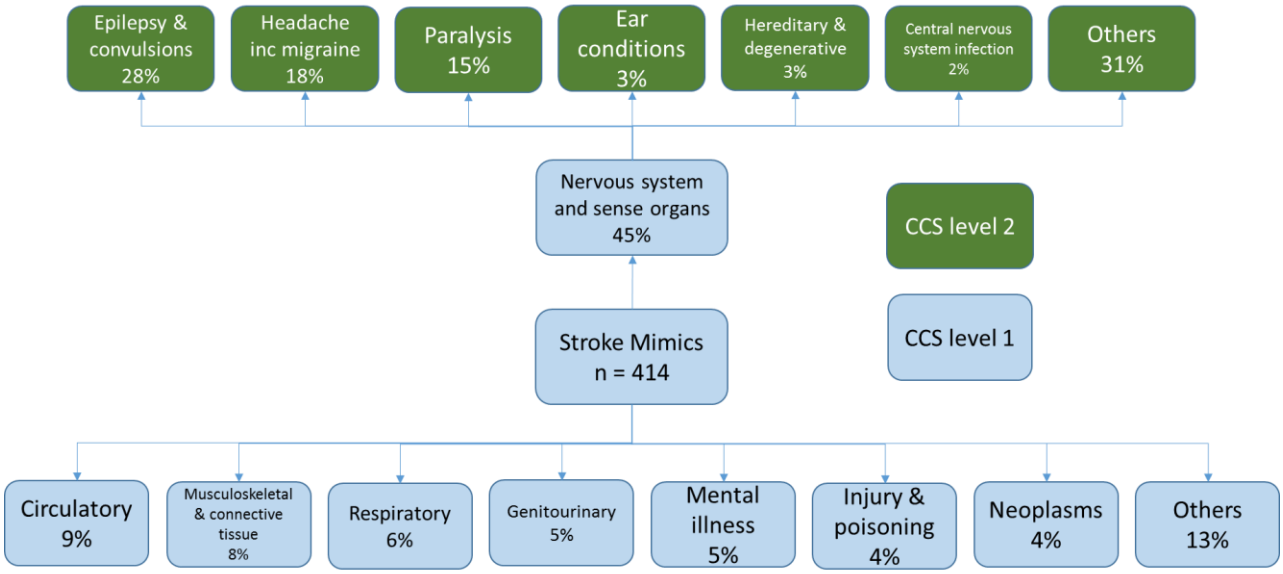


Figure 3.1.3 CDDFT SM diagnoses summarised using CCS codes

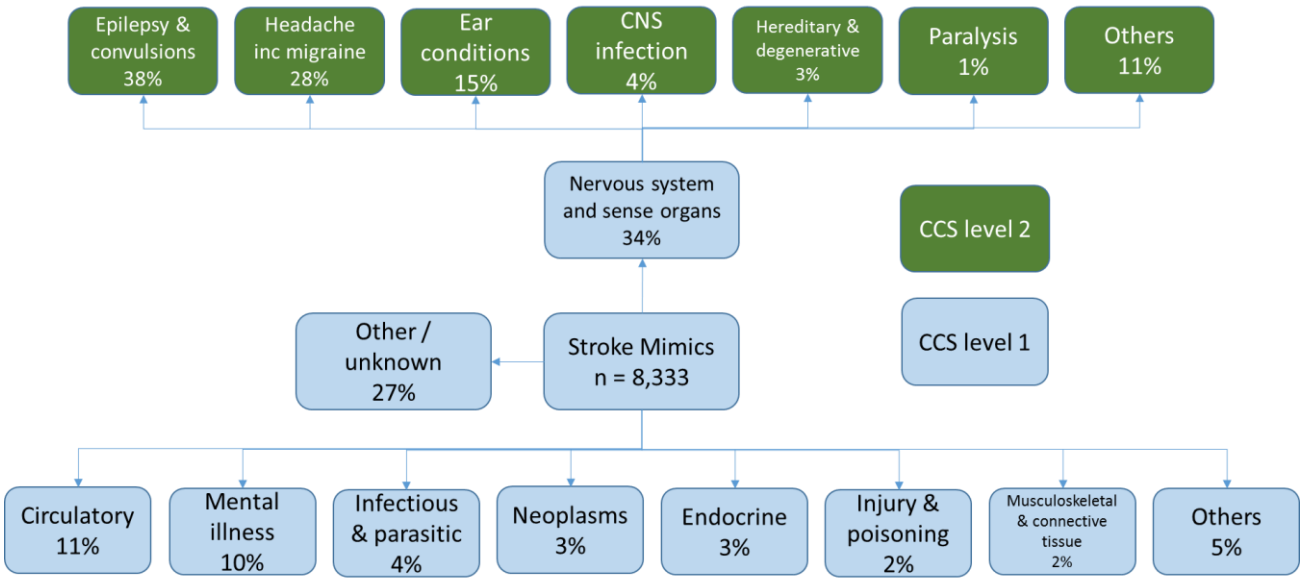


Figure 1.2.3 Taxonomy of SM using CCS codes (repeated from chapter 1.2)

3.1.4.6 Patient characteristics

The demographics of the CDDFT sample are displayed below. 100% of patients had a gender recorded. One patient had no age documented but was recorded as an adult so was included.

Table 3.1.5 Demographics of NEAS suspected stroke patients transported to CDDFT reported by discharge diagnosis

	Total sample	Stroke	SM	P value
Number patients	1,848	1,243	605	-
Mean age (SD)	72.4 (14.5)	74.1 (12.9)	69.0 (16.8)	<0.001
Gender (% male)	48%	49%	46%	0.119

The mean age for males in the CDDFT cohort was 70.5 (stroke 71.4, SM 68.3). The mean age for females in the CDDFT cohort was 74.2 (stroke 76.6, SM 69.6).

3.1.4.7 Physiological observations

The physiological observations recorded on suspected stroke patients transported to CDDFT hospitals are displayed in table 3.1.6 below.

Table 3.1.6 Physiological observations in NEAS data on suspected stroke patients transported to CDDFT reported by discharge diagnosis				
Physiological observation	**% of patients with observation documented**	**Stroke (mean, SD)**	**SM (mean, SD)**	**P value**
BM (mmol/l)	94%	7.7 (3.0)	7.3 (2.6)	0.008
GCS	100%	14 (1.6)	14 (1.9)	0.054
Heart rate	100%	82 (17.6)	84 (18.8)	0.010
Irregular pulse	97%	26%	17%	<0.001
Pain (0-10)	65%	0.3 (1.3)	0.8 (2.0)	<0.001
SaO2	99%	96 (2.6)	96 (3.1)	0.273
Respiratory rate	99%	17 (2.7)	18 (3.4)	0.008
SBP (mmHg)	99%	158 (26.9)	151 (27.3)	<0.001
DBP (mmHg)	99%	88 (16.5)	85 (17.0)	0.005
Temperature (Celsius)	89%	36.5 (0.7)	36.5 (0.9)	0.122

3.1.4.8 Past medical history

The PMH of suspected stroke patients transported to CDDFT are shown in table 3.1.7 below.

Table 3.1.7 Past medical history of NEAS suspected stroke patients transported to CDDFT reported by discharge diagnosis				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
PMH Alcohol misuse	33 (2%)	17 (1%)	16 (3%)	0.052
PMH Angina	192 (10%)	133 (11%)	59 (10%)	0.531
PMH Diabetes	334 (18%)	227 (18%)	107 (18%)	0.763

Table 3.1.7 Past medical history of NEAS suspected stroke patients transported to CDDFT reported by discharge diagnosis cont.				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
PMH Epilepsy	59 (3%)	17 (1%)	42 (7%)	<0.001
PMH Heart failure	68 (4%)	44 (4%)	24 (4%)	0.647
PMH High cholesterol	375 (20%)	270 (22%)	105 (17%)	0.029
PMH Hypertension	674 (37%)	500 (40%)	174 (29%)	<0.001
PMH MI	158 (9%)	110 (9%)	48 (8%)	0.509
PMH Migraine	28 (2%)	17 (1%)	11 (2%)	0.457
PMH Smoking	55 (3%)	42 (3%)	13 (2%)	0.144
PMH Stroke	425 (23%)	220 (18%)	205 (34%)	<0.001
PMH TIA	326 (18%)	199 (16%)	127 (21%)	0.008

3.1.4.9 Clinical signs and symptoms

The signs and symptoms recorded by the paramedics are displayed below.

Table 3.1.8 NEAS observation on suspected stroke patients transported to CDDFT reported by discharge diagnosis				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
Abnormal gait	180 (10%)	129 (10%)	51 (8%)	0.185
AF	259 (14%)	197 (16%)	62 (10%)	0.001
Alcohol/Drug use reported	60 (3%)	34 (3%)	26 (4%)	0.075

Table 3.1.8 NEAS observation on suspected stroke patients transported to CDDFT reported by discharge diagnosis cont.

	Patients with condition (% of total patients)	Stroke (% of stroke patients with condition)	SM (% of SM patients with condition)	P value
Arm weakness*	1182 (64%)	851 (69%)	331 (55%)	<0.001
Chest pain	10 (1%)	4 (<1%)	6 (1%)	0.065
Confusion	493 (27%)	322 (26%)	171 (28%)	0.282
Dizziness	195 (11%)	129 (10%)	66 (11%)	0.727
Eye issues (FT)*	77 (4%)	67 (5%)	10 (2%)	<0.001
Facial droop or weakness	1016 (55%)	724 (58%)	292 (48%)	<0.001
FAST+ve*	919 (50%)	647 (52%)	272 (45%)	0.004
Floppy	82 (4%)	55 (4%)	27 (5%)	0.97
General weakness	381 (21%)	242 (20%)	139 (23%)	0.08
Headache	400 (22%)	229 (18%)	171 (28%)	<0.001
Leg weakness*	893 (48%)	663 (53%)	230 (38%)	<0.001
Nausea or vomiting*	224 (12%)	159 (13%)	65 (11%)	0.206
Neck Stiffness	14 (1%)	5 (<1%)	9 (2%)	0.012
Seizures	46 (3%)	4 (<1%)	42 (7%)	<0.001
Speech symptoms	1255 (68%)	885 (71%)	370 (61%)	<0.001
Syncope	32 (2%)	11 (1%)	21 (4%)	<0.001
Tremors	44 (2%)	17 (1%)	27 (5%)	<0.001
Unconscious	62 (3%)	27 (2%)	35 (6%)	<0.001
Visual disturbances*	179 (10%)	107 (9%)	72 (12%)	0.025

*The same criteria for these characteristics were used as documented in chapters 1.4 and 2.2.

3.1.4.10 Paramedic documentation of impression

Paramedic impression was examined to see if it related to discharge diagnoses. Impression was grouped into three distinct categories:

1. Stroke only = stroke as only suspected diagnosis.
2. Stroke and TIA = stroke and TIA documented as only diagnoses.
3. Stroke plus other = stroke included amongst multiple differential diagnoses.

These three categories of impression were then compared with hospital discharge diagnoses.

Table 3.1.9 Paramedic impression and discharge diagnoses - CDDFT			
Impression	**Total patients**	**Stroke**	**SM**
Stroke only	1,413	1,023 (72%)	390 (28%)
Stroke and TIA	140	88 (63%)	52 (37%)
Stroke plus others	295	132 (45%)	163 (55%)

The stroke plus other impression category included stroke plus a median of 2 additional impressions (range 1-8, IQR 1-2). Stroke patients with impression of 'stroke plus other' had 30 different impressions documented in addition to stroke. SM patients with impression 'stroke plus other' had 37 different impressions documented in addition to stroke.

3.1.4.11 STEAMv2 performance in the validation dataset

Applying STEAMv2 to the validation dataset generated the following results.

Table 3.1.10 STEAMv2 output when applied to the validation dataset

STEAMv2 score	Total patients	Stroke	SM
0	1,606	1,143	463
1	202	94	108
2	39	6	33
3	0	0	0
4	1	0	1

Note: STEAMv2 positive rows are shaded.

STEAMv2 identified 34 SM patients and 6 stroke patients in the validation dataset using 2+ as the cut-off. The characteristics that triggered STEAMv2 (n=34, true SM patients) were:

- SBP + FAST-ve = 1 patient
- Temperature + HR + Age<40 = 1 patient
- Seizures + PMH epilepsy = 8 patients
- Seizures + PMH Epilepsy + Age<30 = 1 patient
- Seizures + FAST-ve = 4 patients
- Seizure + Age<40 = 1 patient
- Age<30 = 12 patients
- Age<40 + FAST-ve = 5 patients
- Headache + PMH migraine + Age<40 = 1 patient

The STEAMv2 false positives (n=6, true stroke patients) triggered the following combinations of characteristics:

- Age<30 = 2 patients
- Age<40 + FAST-ve = 2 patients
- Seizures + FAST-ve = 1 patient
- Headache + PMH Migraine + FAST-ve = 1 patient

None of the STEAMv2 false positives (n=6) were recorded as thrombolysed.

Scoring ≥2 on STEAMv2 generated the following performance characteristics, with 95% CI, when applied to the CDDFT validation dataset:

- Sensitivity 5.6% (3.9-7.8)
- Specificity 99.5% (99.0-99.8)
- Positive predictive value (PPV) 85.0% (71.0-93.1)
- Negative predictive value (NPV) 68.4% (68.0-68.8)
- Positive likelihood ratio (PLR) 11.6 (4.9-27.6)
- Negative likelihood ratio (NLR) 1.0 (0.9-1.0)
- Odds ratio (OR) 12.3 (5.1-29.4)

3.1.4.12 Comparing the development, refinement and validation datasets

The development dataset (NHCT: 1,650 suspected stroke patients with a 40% SM rate) was described in chapter 1.5.

The refinement dataset (NHCT, NUTH and NTEES: 3,797 suspected stroke patients with a 41% SM rate) was described in chapter 2.2.

The external validation dataset (CDDFT) included 1,848 suspected stroke patients with a 33% SM rate.

3.1.4.13 Patient demographics

The demographics of the suspected stroke cohorts are displayed in table 3.1.11.

Table 3.1.11 Demographics of NEAS suspected stroke patients reported by discharge diagnosis

Dataset		Suspected stroke	Stroke	SM	P value
Development	**Patients**	1,650	989 (60%)	661 (40%)	-
	Mean age (SD)	75.3 (13.4)	77.0 (11.7)	72.8 (15.3)	<0.001
	Gender (% male)	47%	50%	41%	<0.001
Refinement	**Patients**	3,797	2,240 (59%)	1,557 (41%)	-
	Mean age (SD)	73.6 (14.3)	75.6 (12.4)	70.8 (16.2)	<0.001
	Gender (% male)	48%	52%	44%	0.001
Validation	**Patients**	1,848	1,243 (67%)	605 (33%)	-
	Mean age (SD)	72.4 (14.5)	74.1 (12.9)	69.0 (16.8)	<0.001
	Gender (% male)	48%	49%	46%	0.119

The mean age was statistically different ($p<0.05$) in all three diagnostic groups between the refinement and validation datasets. There was no statistical difference between the gender split in any of the diagnostic groups.

3.1.4.14 Source of diagnoses of suspected stroke patients

The sources of the diagnoses for the NEAS suspected stroke patients in the development, refinement and validation datasets are reported in table 3.1.12.

Table 3.1.12 Sources of diagnoses for suspected stroke patients

	Development	Refinement	Validation
Suspected stroke patients	**1,650**	**3,797**	**1,848**
Stroke based on SSNAP	839 (85%)	1,913 (85%)	915 (74%)
Stroke based on HES	66 (7%)	163 (7%)	172 (14%)
TIA based on HES	84 (8%)	164 (7%)	156 (13%)
Total Stroke (inc TIA)	**989**	**2,240**	**1,243**
SM based on HES	526 (80%)	990 (64%)	414 (68%)
Assumed SM	135 (20%)	567 (36%)	191 (32%)
Total SM	**661**	**1,557**	**605**

Note. Percentages refer to the percentage of the relevant diagnostic group (stroke or SM) for each hospital i.e. 85% of 989 stroke diagnoses in the development cohort were based on SSNAP.

3.1.4.15 Assumed SM patients

SM patients were identified by either confirmed non-stroke diagnosis (any ICD-10 code other than I61, I63, I64 or TIA codes G458 and 459) in hospital HES systems or assumed based on inability to match with either SSNAP or HES. Patients with an assumed SM diagnosis are compared with patients with a confirmed SM diagnosis in table 3.1.13 below.

Table 3.1.13 Comparison of patients with confirmed SM diagnoses versus assumed SM diagnoses			
	Diagnoses	**Age (mean, SD)**	**Gender (% Male)**
Development (n=661)	**Confirmed (n=526)**	74.0 (14.7)	41
	Assumed (n=135)	67.5 (17.4)	41
Refinement (n=1,557)	**Confirmed (n=990)**	72.2 (15.6)	43
	Assumed (n=567)	68.3 (17.0)	46
Validation (n=605)	**Confirmed (n=414)**	67.8 (16.9)	45
	Assumed (n=191)	71.2 (17.1)	47

Patients in the refinement dataset with a confirmed SM diagnosis were significantly older (independent samples t-test, $p<0.001$) than patients in the validation dataset. Patients with an assumed SM diagnosis were significantly younger (independent samples t-test, $p=0.020$) in the refinement dataset than patients in the validation dataset. There were no significant differences between the refinement and validation cohorts in terms of gender (chi squared test, confirmed diagnosis $p=0.794$, assumed diagnosis $p=0.583$).

3.1.4.16 STEAMv2 results in datasets

The results of applying STEAMv2 to the refinement and validation datasets are shown in table 3.1.14.

Table 3.1.14 Suspected stroke patients displayed by number of STEAM characteristics				
Dataset	**Number of positive STEAMv2 characteristics**	**Total patients**	**Stroke (n, %)**	**SM (n, %)**
Refinement (n=3,797)	0	3,283	2,070 (63)	1,213 (37)
	1	421	162 (38)	259 (62)
	2	84	8 (10)	76 (90)
	3	8	0	8 (100)
	4	1	0	1 (100)
Validation (n=1,848)	0	1,606	1,143 (71)	463 (29)
	1	202	94 (47)	108 (53)
	2	39	6 (15)	33 (85)
	3	0	0	0
	4	1	0	1 (100)

Note: STEAMv2 positive rows are shaded.

3.1.4.17 STEAMv2 performance in datasets

The performance of STEAMv2 in the validation dataset is described alongside the performance in the refinement dataset in table 3.1.15. STEAMv1 performance in the refinement and validation datasets is also displayed for comparison.

Table 3.1.15 STEAM tool performance in the validation and refinement datasets				
		Validation dataset	**Refinement dataset**	**Change**
STEAMv2	**Sensitivity (95% CI)**	5.6% (3.9-7.8)	5.5% (4.4-6.7)	+0.1%
	Specificity (95% CI)	99.5% (99.0-99.8)	99.6% (99.3-99.9)	-0.1%
	PPV (95% CI)	85.0% (70.5-93.1)	91.4% (83.8-95.6)	-6.4%
STEAMv1	**Sensitivity (95% CI)**	10.6% (8.2-13.3)	11.1% (9.5-12.7)	-0.5%
	Specificity (95% CI)	98.0 (97.1-98.7)	98.3% (97.6-98.8)	-0.3%
	PPV (95% CI)	71.9 (62.0-80.1)	81.5% (75.8-86.1)	-9.6%

3.1.5 Discussion

This chapter describes the validation of STEAMv2. A new dataset was created linking NEAS suspected stroke patients with hospital diagnoses from CDDFT in order to test the performance of STEAMv2 on patients who were not involved in the development or refinement process. STEAMv2 performed consistently in terms of sensitivity and specificity but the PPV dropped from 91.4% in the refinement dataset to 85.0% in the validation dataset.

The validation dataset was the largest cohort from any individual trust and it differed from the refinement dataset in a number of ways. Patients in the validation dataset were younger than the patients used to develop STEAMv2. Stroke and SM patients were similar in terms of gender unlike the refinement dataset where there was a significant difference. The demographics of the assumed SM patients, which were examined separately, also showed a difference to the refinement dataset. Assumed SM patients were older than confirmed SM patients in the validation dataset compared to the refinement dataset where assumed SM patients were younger. The increased age of the assumed SM patients in the validation dataset could suggest that there were more stroke patients in this group as the overall populations were similar in terms of age. However, without true diagnoses for the assumed SM patients the cause of this difference is difficult to isolate.

The validation dataset had a lower SM rate (33%) than the refinement dataset (41%) and CDDFT had the lowest SM rate of the four trusts who were involved. CDDFT had a slightly different process for admitting suspected stroke patients to the other three trusts. Due to the need to bypass one CDDFT hospital to access the stroke unit, NEAS paramedics can telephone the CDDFT stroke unit and discuss the suspected stroke patient before transporting them. This input may have influenced practice in crews local to CDDFT by making paramedics more cautious about labelling patients with less clear presentations as stroke. The younger age of CDDFT suspected stroke patients could also mean less very elderly patients with multiple comorbidities were considered as suspected stroke, or accepted by the stroke unit, due to the local redirection process.

The stroke diagnoses in the validation dataset presented in a different pattern to the development and the refinement datasets with less patients being directly matched with

SSNAP and more stroke diagnoses being found via HES. The TIA rate in the validation dataset was also nearly double the rate of the development or refinement datasets.

The differences in demographics, SM rate and pattern of diagnostic sources suggests that suspected stroke patients in the validation dataset were a slightly different population to the suspected stroke patients in the refinement dataset where the demographics, SM rates and diagnostic patterns were more consistent across the three trusts included. The discharge data collection processes varied between the four acute trusts depending on the level of technical support available so there may have been factors specific to the CDDFT data that influenced the SM rate. These differences could have influenced the performance of STEAMv2 in the validation dataset.

STEAMv2 performed consistently in terms of sensitivity and specificity in the validation dataset but the PPV dropped from 91.4% in the refinement dataset to 85.0% in the validation dataset. This PPV value is still above the original STEAMv1 value from the development dataset (84%) which was considered acceptable by participants in the first round of focus groups (chapter 2.1). The lower PPV may also have been influenced by the lower rate of SM in the validation dataset. Another reason for this may have been the higher rate of FAST-ve stroke patients in the validation dataset (validation 54%, refinement 43%). This influenced the reduced PPV of STEAMv2 in the validation dataset as two-thirds of the false positives were FAST-ve strokes compared to only half in the refinement dataset.

One of the issues with prognostic models like STEAMv2 that prevents them being adopted into clinical practice is lack of validation (Altman *et al.*, 2009). The TeleStroke Mimic score (Ali *et al.*, 2014), described in chapter 1.1, (which included age and seizures similar to STEAMv2) was the only SM tool with repeated validation studies. The TeleStroke Mimic score had internal and external validation in the original development paper and reported performance in terms of AUC of 0.75 for the development and 0.71 and 0.77 for the validation cohorts. It was then validated in an external telehealth cohort with an AUC of 0.70 (Ali *et al.*, 2016) and a mobile stroke unit study (Ali *et al.*, 2018) which reported an AUC of 0.74. These values compare to the AUC for STEAMv2 of 0.75 (refinement) and 0.77 (validation). More recently the TeleStroke Mimic score has been evaluated in the pre-hospital setting in Germany (Geisler *et al.*, 2018). This study used data collected from a previous mobile stroke unit study to test the TeleStroke Mimic score. They found similar

demographic and PMH risk factors, a similar pattern of SM aetiologies and the same inverse relationship between sensitivity and specificity.

3.1.5.1 Strengths and limitations

The validation data were based on suspected stroke patients transported to CDDFT which provided a new dataset and was therefore classed as external validation. A future study could consider the performance of STEAMv2 in a different ambulance service to repeat the validation and increase the generalisability.

Despite the large number (n=1,848) of patients in the CDDFT dataset, the differences in demographics, characteristics and patterns of diagnoses mean that this is a slightly different population to the refinement population. This could be considered fortuitous as it allowed STEAMv2 to be tested in a slightly different population, but also leads to cautious interpretation as there may be differences in the local processes, paramedic behaviour or other unknown factors, that influenced the composition of the stroke and SM populations.

3.1.6 Conclusions

Altman et al stated that '*simplicity and reliability of measurements are important criteria in developing clinically useful prognostic models*' (Altman *et al.*, 2009). STEAMv2 is a simple tool which was validated in this new dataset. Despite some differences between the validation dataset and the refinement dataset, STEAMv2 performed consistently apart from a small reduction in the PPV.

3.1.7 Summary

STEAMv2 has been developed, refined and validated using data from NEAS linked with discharge diagnoses from four acute trusts in the North East. The process of developing STEAMv2 was informed by focus groups with paramedics and clinicians, and usability testing by NEAS paramedics. The potential impact of STEAMv2 will be explored in the next chapter which will use simple modelling to consider potential outcomes. This is followed by chapter 3.3 which reports the findings from a second phase of focus groups including the views of paramedics and clinicians from the North East and the North West.

Chapter 3.2 Modelling of potential impact of STEAMv2

3.2.1 Introduction

This chapter describes how the potential impact of introducing STEAMv2 into clinical practice was considered. Moons et al (Moons *et al.*, 2009a) described three options for assessing the impact of a prognostic tool like STEAMv2: firstly, use conclusive evidence from development and validation studies to introduce the tool and observe its impact in practice; secondly, conduct further pragmatic research to expand the evidence base; thirdly, use modelling to explore the possible consequences of applying the tool. This chapter uses the third approach and describes a simple decision tree modelling approach. This modelling was then used to consider the impact that application of STEAMv2 could have across a range of care delivery outcomes.

3.2.2 Chapter aims and objectives

The aim of this chapter is to model and consider what impact STEAMv2 could have if it was applied in clinical practice.

The objectives are:

- Apply STEAMv2 to a simple model of pre-hospital stroke care.
- Discuss how introducing STEAMv2 into pre-hospital stroke care could impact on stroke outcomes.

3.2.3 Methods

Simple models were developed to conceptualise and explore the impact of STEAMv2 on pre-hospital stroke care. Pitt et al described three modelling approaches commonly used in healthcare research: qualitative modelling, mathematical modelling, and simulation (Pitt *et al.*, 2016). As the purpose here was to understand the impact of an additional SM identification step upon the hyper acute stroke system, which includes pre-hospital and the acute hospital treatment, a simple mathematical modelling approach was chosen using discrete patient groups rather than using individual patient data in a simulation. This allowed the main components of the clinical care process to be represented and thereby generate

insight into patient pathways, the practical impact of key decisions and the resulting trade-offs.

The pre-hospital and hospital process was defined by a conceptual model to inform the creation of a mathematical decision tree representing the key decisions in pre-hospital stroke care. Adjusting the variables representing characteristics such as accuracy of stroke identification and application of the STEAMv2 tool allowed various system configurations to be considered.

Four outcome categories are discussed related to the performance of a hyper-acute stroke system including: reperfusion treatment rates and speeds; disability impact; resource implications; and health economic outcomes (Monks *et al.*, 2015).

The overall process that will be discussed is summarised in figure 3.2.1 below.

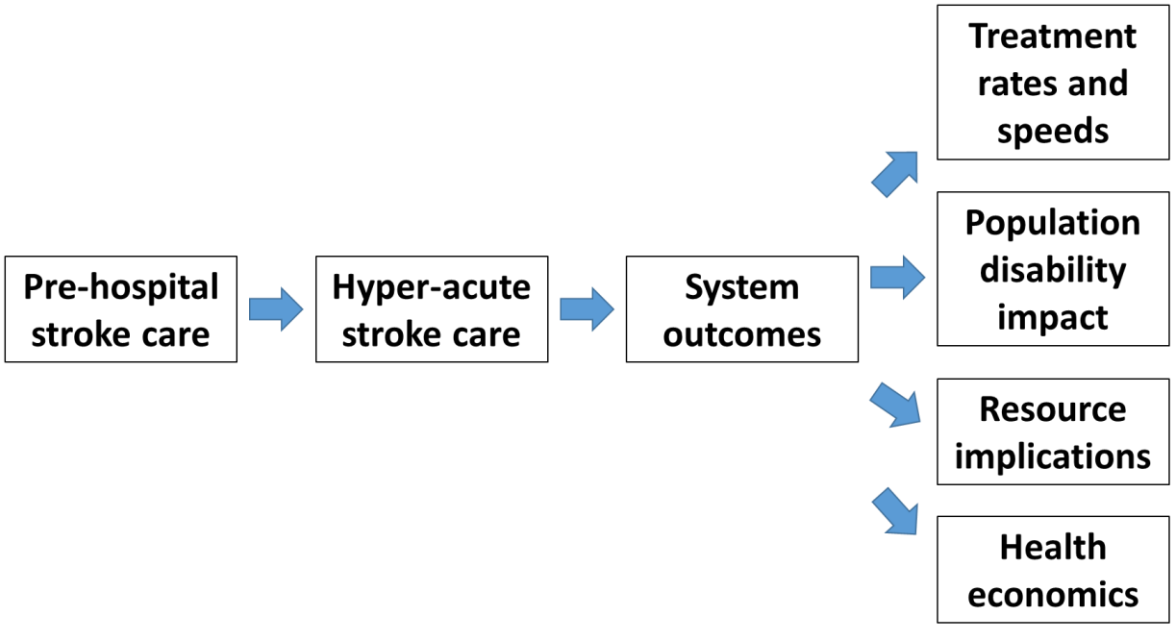


Figure 3.2.1 Stroke patient pathway from pre-hospital stroke care to system outcomes

3.2.4 Conceptual model of pre-hospital stroke care

Existing models describing acute stroke care were examined to help define the most relevant components of the proposed clinical pathway. Some models identified that the ambulance service was one of multiple routes by which stroke patients could arrive at hospital (Monks *et al.*, 2012; Doggen *et al.*, 2016), whereas others simply incorporated a time delay element in the pre-hospital phase without specifying a mode of admission (Bayer

et al., 2010; Lahr *et al.*, 2013; Jacobson *et al.*, 2015). For this purpose, modes of admission other than ambulance were not relevant as their care pathway would not be affected by the introduction of a paramedic SM tool. Churilov et al (Churilov *et al.*, 2013) and Sheppard et al (Sheppard *et al.*, 2015a) modelled the pre-hospital phase of acute stroke care and included pathways representing the potential for paramedics to recognise or not-recognise stroke.

A simple conceptual model of the pre-hospital stroke pathway was created (figure 3.2.2) based upon the UK ambulance clinical practice guidelines (Association of Ambulance Chief Executives and Joint Royal Colleges Ambulance Liaison Committee, 2016). Pre-alerting was the only action included, as it is the only intervention other than stroke recognition in common paramedic practice that directly impacts on processes associated with stroke patient outcomes. Pre-alerting is discussed further below. As the focus of the model was the impact of paramedic identification of stroke versus SM it does not include the initial 999 call taker identification of stroke.

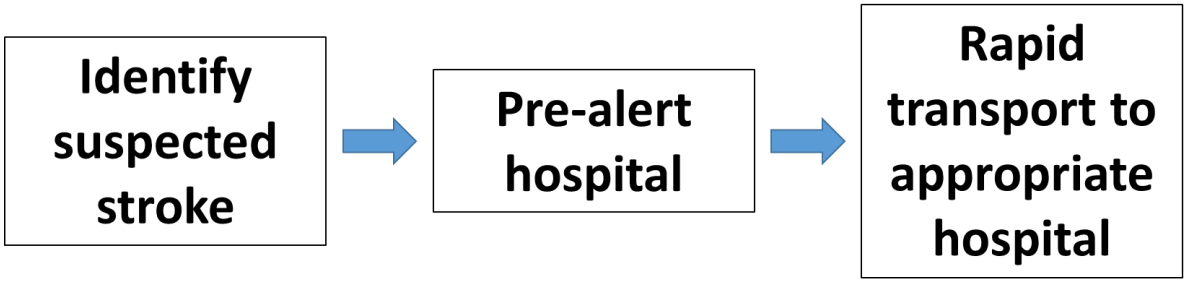


Figure 3.2.2 Simple conceptual model of pre-hospital stroke pathway 1

The model was then expanded to consider how suspected stroke patients would be directed towards hospital services, the actions that could be taken in the pre-hospital setting and the potential destinations (figure 3.2.3). Each box represents a possible choice or outcome so patients may or may not be pre-alerted.

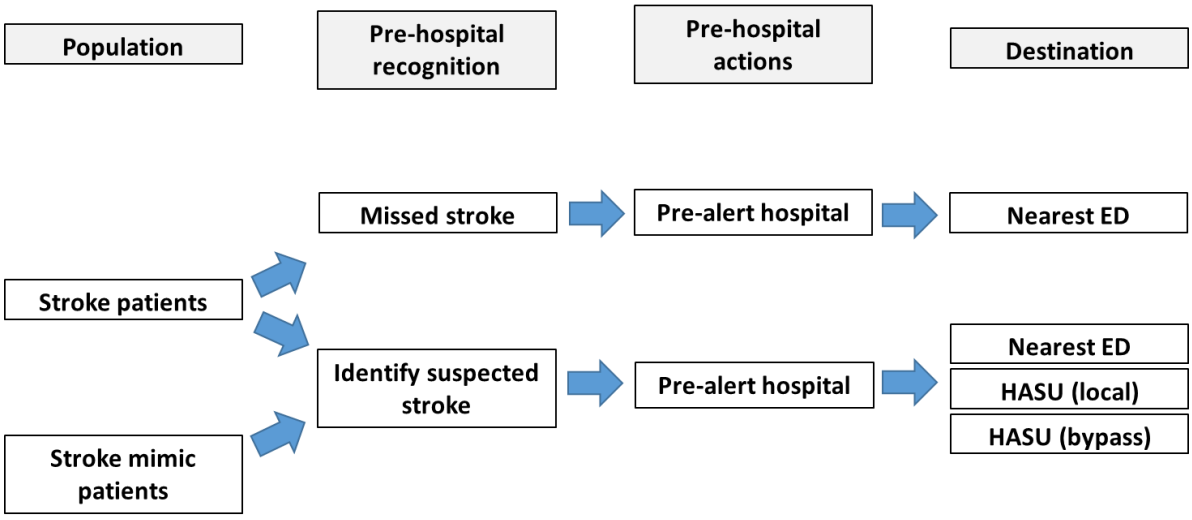


Figure 3.2.3 Simple conceptual model of pre-hospital stroke pathway 2

This simple conceptual model represents the key decisions and stages in the pre-hospital flow of suspected stroke patients and shows the potential outcomes in terms of the patient's final destination. The SM tool was added to the pre-hospital stroke recognition stage (figure 3.2.4), where it can be used in combination with normal pre-hospital stroke recognition tools. This permits representation of the most relevant pathways which could occur including the additional pre-hospital identification process e.g. a stroke patient (population) could be identified as stroke and not SM (pre-hospital recognition) who is then pre-alerted (pre-hospital action) to the local HASU (destination).

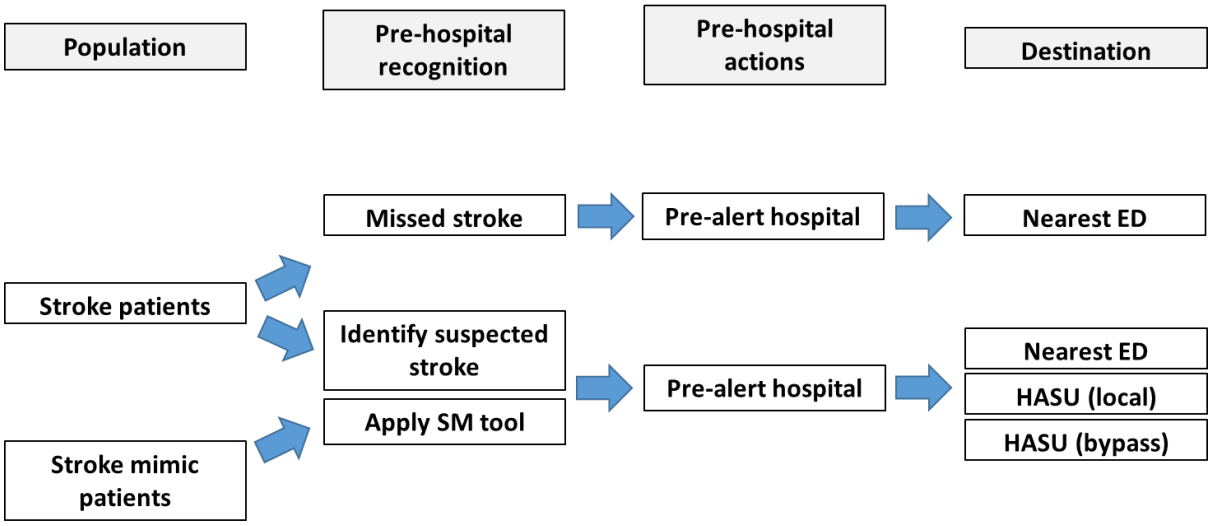


Figure 3.2.4 Simple conceptual model of pre-hospital stroke pathway 3

3.2.4.1 Population

The population considered by this model could be simply stated as 'suspected stroke population' but this fails to consider that there are a population of stroke patients who will not be recognised (missed stroke or "stroke chameleons"). This group of patients need to be acknowledged when considering the number of patients who may be affected by any change to pre-hospital stroke pathways.

3.2.4.2 Pre-hospital recognition

Pre-hospital stroke recognition is based on the FAST in the UK, but this model could represent any stroke identification tool or process. The addition of the SM tool to this stage of the process shows how it is intended to work in conjunction with the initial stroke identification and how the combination would affect the actions which follow.

3.2.4.3 Pre-hospital actions

The only pre-hospital action in the current model is whether the patient is pre-alerted into hospital or not. It is impossible to say whether stroke chameleons, SM patients or non-strokes would be pre-alerted to hospital as it depends on the overall condition of the patient, the attending paramedic and the local pathways and procedures. Pre-alerting is also influenced by the patient's destination as some receiving units will require a pre-alert and others will not. The impact of pre-alerting is considered further under the treatment rates and speeds outcomes section.

3.2.4.4 Destination

Transportation to either ED or HASU are the two options available to paramedics who have identified a suspected stroke patient. The HASU may be at the local hospital or it may be at a distant hospital depending on the patients' location and the organisation of services in that area. Therefore, there are three potential destinations included in the model: nearest ED; local HASU; or distant HASU.

3.2.5 Decision tree model of pre-hospital stroke recognition

Based on the conceptual model described above a mathematical model of pre-hospital stroke recognition was constructed to represent how a SM tool impacts on pre-hospital stroke recognition which is the first two components of the conceptual model i.e. definition

of the stroke and SM population. The focus is on these early stages as they determine the following course of action and the destination, in addition destination only becomes relevant when there are multiple possibilities. This model was structured as a decision tree (as shown in figure 3.2.5) with the underlying algorithm performed by Microsoft Excel. Decision tree modelling has previously been used to explore pre-hospital treatment of acute stroke (Lorenz *et al.*, 2015), optimizing stroke care for thrombolysis (Penaloza-Ramos *et al.*, 2014), and the impact of mechanical thrombectomy (McMeekin *et al.*, 2017).

The decision tree is a very simple representation of the pre-hospital recognition of stroke and the application of a SM tool. It does not account for any information which could influence that decision in clinical practice e.g. paramedic seniority or the patient's combination of symptoms. This decision tree model was then used to consider the application of STEAMv2 in three scenarios:

1. A theoretical population of 1,000 stroke patients.
2. The North East region.
3. The whole of the UK.

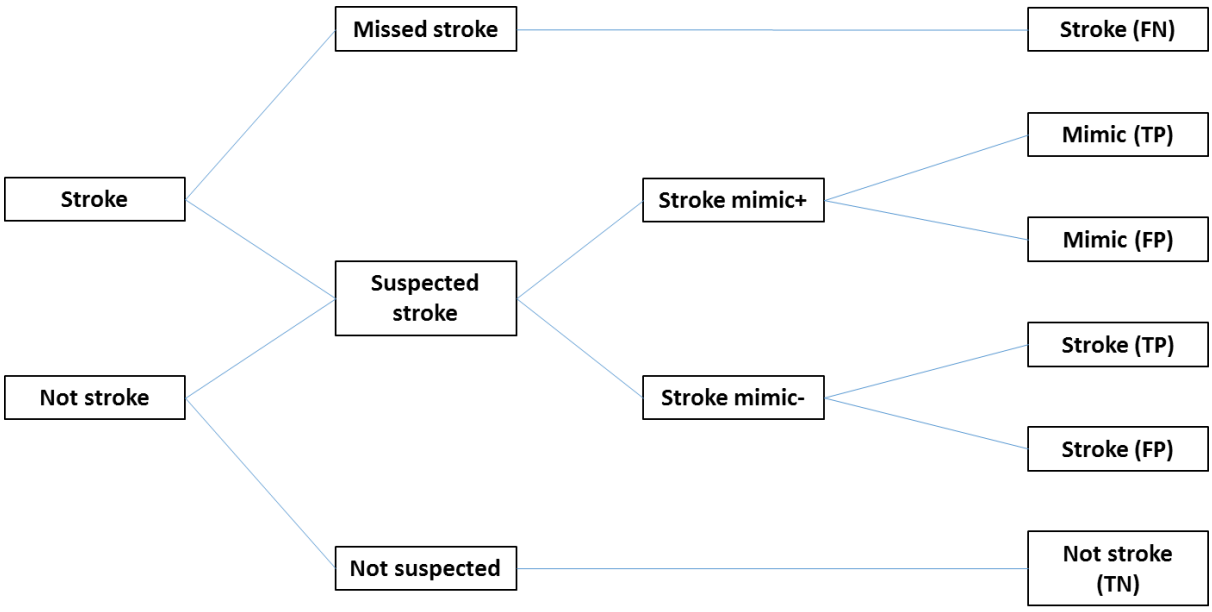


Figure 3.2.5 Decision tree representation of pre-hospital stroke recognition (FN, false negative; TP, true positive; FP false positive; TN, true negative)

3.2.6 Scenario 1: Applying STEAMv2 to a theoretical population

The stroke population was set at 1,000 patients as a population size that represents one year of HASU stroke admissions, and is a convenient unit for scaling up and down. In the scenario below the model is parameterised with variables reflecting the probabilities and consequences of key decisions within each stage. The data used to parameterise decisions are described below in table 3.2.1.

Table 3.2.1 Values used in scenario 1

Parameter	Value(s)	Source(s)
Stroke population	1,000	
SM rate	40%	Chapters 1.4, 2.2
Sensitivity pre-hospital stroke recognition	79%	Based on FAST. (Harbison *et al.*, 2003; Rudd *et al.*, 2016a)
PPV pre-hospital stroke recognition	60%	Chapters 1.4, 2.2
Sensitivity pre-hospital SM recognition	5%	Chapter 2.2 (STEAMv2)
PPV pre-hospital SM recognition	91%	Chapter 2.2 (STEAMv2)

Application of STEAMv2 was modelled reflecting the following degrees of implementation within the ambulance service:

- Scenario 1a. No SM tool (current standard practice).
- Scenario 1b. 50% STEAMv2 tool use.
- Scenario 1c. 100% STEAMv2 tool use.

Table 3.2.2 Outputs from scenario 1			
	Scenario 1a (0 SM tool use)	**Scenario 1b (50% STEAMv2 use)**	**Scenario 1c (100% STEAMv2 use)**
True positive: stroke	790	789	787
False negative: stroke	210	210	210
False positive: SM	316	303	290
True positive: SM	0	13	26
False positive: stroke	0	1	3
Overall sensitivity of stroke recognition	79%	79%	79%
Overall PPV of stroke recognition	60%	61%	61%
Combined PPV of stroke and SM recognition	60%	61%	62%

This simple scenario shows the small numbers of patients who would be identified by STEAMv2 (n=29 if 100% use) and the very small impact this has on the predictive value of pre-hospital stroke recognition overall.

3.2.7 Scenario 2: Applying STEAMv2 in the North East

Scenario 1 demonstrated that STEAMv2 had minimal impact on stroke recognition when a population of 1,000 stroke patients was considered but it does not account for pre-hospital actions, different destinations or a system with multiple admission routes to hospital. The context in which a SM identification tool such as STEAMv2 becomes potentially more useful is across a region with multiple hospitals and the potential to bypass local hospitals to access distant HASUs. In this situation SM identification becomes potentially more impactful. Whole-system simulation modelling of patient transportation to multiple hospitals requires consideration of a large number of variables including:

- Local admission criteria
- Local pre-alert requirements
- Travel times and distances
- Time taken and delays at various stages
- Secondary transfers for stroke patients transported to a hospital without stroke services
- Repatriation criteria.

Modelling these variables would be necessary to understand the impact of introducing an additional decision stage for SM identification into a more realistic system with multiple hospitals, but this would introduce far more complexity than could be factored into a simple analytical mathematical model. Multiple hospital systems would also be difficult to generalise as they would be heavily influenced by local geography and pathways.

A simple decision tree like figure 3.2.5 cannot adequately represent a regional pathway due to the multiple destinations and the factors described above, however if the region is considered as a single entity then a simple model can be applied.

3.2.7.1 The North East

The North East region served by NEAS stretches from the borders of Scotland in the north to Teesside in the south and across to Cumbria in the west. This area covers 3,230 square miles and includes 2.71 million people. In 2018 the North East included eight acute hospital trusts, nine EDs and six acute stroke units (North East Ambulance Service NHS Foundation Trust, 2018).

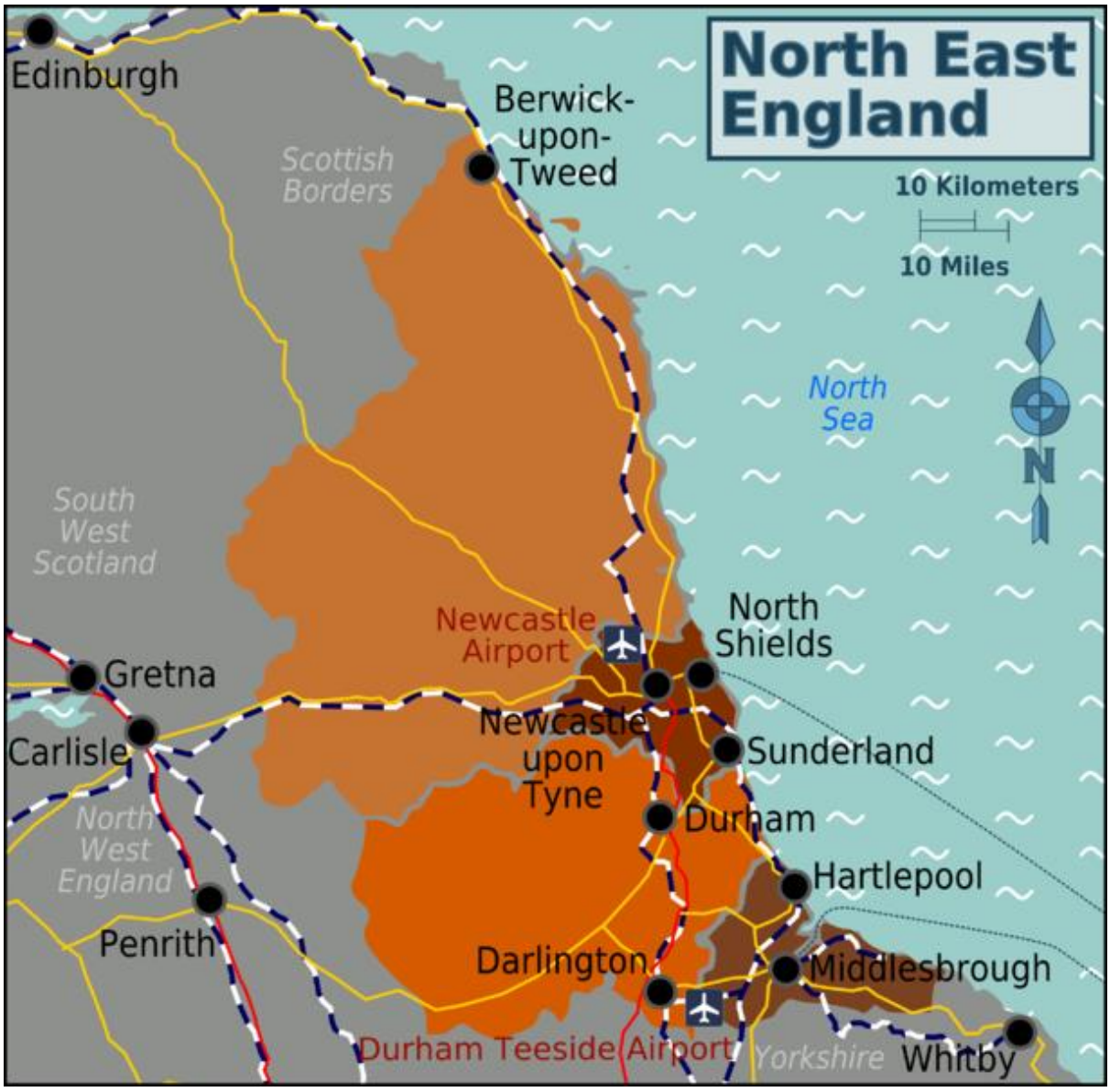


Figure 3.2.6 Map of the North East (Wikivoyage, 2006)

Three out of nine North East EDs do not accept stroke patients, these are the Queen Elizabeth Hospital in Gateshead (QE), South Tyneside District General Hospital (STGH) and Darlington Memorial Hospital (DMH). These three hospitals serve approximately 490,000 people (QE 200k, STGH 140k, DMH 150k) which is 18% of the North East population. The NEAS stroke pathway redirects suspected stroke patients in the catchment areas of these three hospitals to the nearest hospital with a HASU.

The NEAS data on regional suspected stroke admissions (chapter 1.4) reported 24,764 patients attended by NEAS over three years. Based on this, the mean number of suspected stroke patients attended each year was 8,254.

Data from the North East Stroke Improvement Network estimated 13 stroke admissions per day across the North East. This equates to 4,745 stroke admissions per year. If a 40% SM rate is assumed (based on chapters 1.4 and 2.2) then the total suspected stroke admissions would be 7,908 per year.

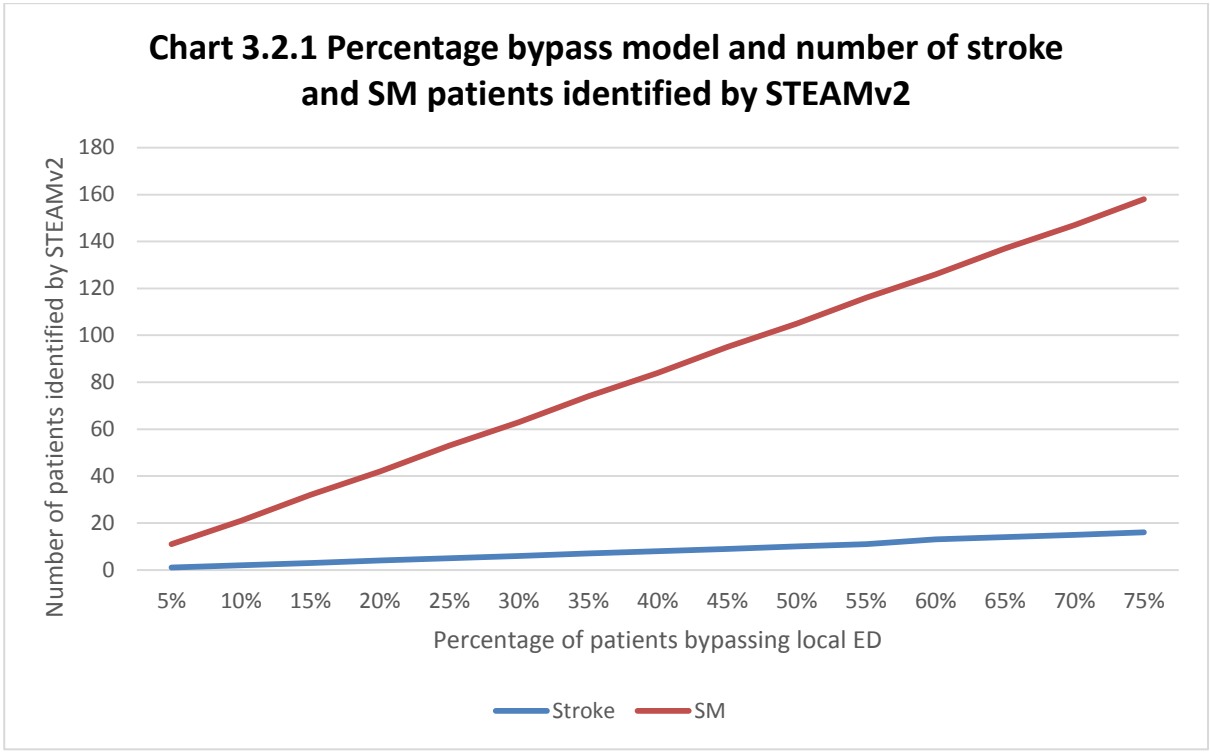
Based on these data, a reasonable approximation for suspected stroke admissions in the North East region is 8,000 per year.

3.2.7.2 STEAMv2 impact on the North East

The impact of applying STEAMv2 to patients who currently bypass their local ED to access HASU care in the North East region can be modelled with the following assumptions based on the 2018 organisation of stroke services:

- 8,000 annual suspected stroke admissions
- 40% SM rate
- 18% bypass rate
- Pre-hospital stroke identification (FAST) = 79% sensitive, 60% PPV
- STEAMv2 = 5% sensitive, 91% PPV
- 100% implementation.

If STEAMv2 was only applied to the 18% of suspected stroke patients that could potentially bypass a local ED (n=1,440) then 42 patients would be identified by STEAMv2 comprising 38 SM and 4 true stroke patients. If more services moved towards centralisation and local bypass, STEAMv2 would affect an increasing number of patients. The results of calculating these figures, using the assumptions stated above, over a range of bypass activity from 5-75% are displayed in chart 3.2.1.



3.2.8 Scenario 3: Applying STEAMv2 to the UK population

The impact of STEAMv2 on stroke admissions across the UK can be considered by scaling up the simple regional model used above. If the following assumptions are made:

- 100,000 strokes per year
- 40% SM rate
- 18% bypass rate
- Pre-hospital stroke identification = 79% sensitive, 60% PPV
- STEAMv2 = 5% sensitive, 91% PPV
- 100% implementation

If STEAMv2 was applied to all suspected stroke patients then it would identify 2,893 patients of which 2,633 would be SM and 260 would be stroke patients. If an 18% bypass rate was assumed to identify patients who may be transported to a different hospital based on STEAMv2 application, then the national patient population affected is 520 patients including 474 SM and 46 stroke patients.

3.2.9 Discussion

This chapter aimed to model what impact STEAMv2 would have on pre-hospital stroke recognition if it was applied in clinical practice. A conceptual model of pre-hospital stroke care was developed which informed a mathematical model which showed that applying STEAMv2 in clinical practice would affect the admission destination for a small number of patients. However to make a judgement about its value, the impact on patient and system outcomes needs to be considered relative to the simplicity and low cost of the additional assessment step. The potential impact of pre-hospital SM identification on the four hyper-acute stroke system outcomes identified by Monks et al (Monks *et al.*, 2015): treatment rates and speeds; population disability impact; resource implications; and health economics, are discussed with reference to the simple models developed above.

3.2.9.1 Treatment rates and speeds

The key treatment for acute ischaemic stroke patients is thrombolysis. Although 15-20% of ischaemic stroke patients are expected to be eligible for thrombolysis, only 11-12% were treated with thrombolysis in the UK (RCP, 2017a). Thrombolysis rates are linked to speed of access to the treatment due to the 4.5 hour treatment window and the clear association between time since onset and benefit (Emberson *et al.*, 2014). The pre-hospital factors that impact on the time to treatment include identification of stroke, the time spent in the pre-hospital phase and whether or not the paramedic pre-alerts the patient.

3.2.9.2 Missed stroke

The discussion so far has focussed on the impact on patients diagnosed as stroke by ambulance services but there are patients where the diagnosis is missed (stroke chameleons) in the pre-hospital setting.

Richoz et al (Richoz *et al.*, 2015) described the outcomes of stroke chameleons attending a university hospital in Switzerland. They discussed how missed stroke diagnoses impacted on patient outcomes by missed thrombolysis opportunities in 23% of patients, delayed access to specialist care and extended the time before secondary prevention was implemented. Stroke chameleons had a lower chance of a favourable outcome (modified Rankin Scale (mRS) <3) and increased mortality rates compared to recognised stroke patients. Arch et al (Arch *et al.*, 2016) reported on patients whose stroke diagnosis was initially missed in the ED.

In this population they showed that patients with an initially missed stroke diagnosis had a longer stay in hospital (6.9 days vs 5.9 days) and a higher rate of readmission within 60 days (33% vs 17%). Therefore improving overall identification of genuine stroke remains a priority.

Efforts to improve the pre-hospital detection of stroke by introducing tools like FAST-AVVV (ataxia, vomiting, vertigo, visual deficit) or other tools including symptoms aimed at identifying posterior stroke may reduce the rate of missed strokes. However, these would potentially increase the SM rate. An expanded initial identification tool, with higher sensitivity but lower specificity, could be used in sequence with a tool like STEAMv2 where the combination may provide an improvement in overall performance.

3.2.9.3 Pre-hospital treatment times

Internal data from NEAS showed that between March 2017 and February 2018 the mean call to ambulance arrival was 19 minutes, the mean on scene time was 29 minutes and the mean travel time to hospital was 15 minutes for stroke patients. Combining these figures gives a mean call to hospital time of 63 minutes.

The NEAS figures are slightly higher than figures reported by other UK ambulance services. A report by London Ambulance Service (LAS) (Clinical Audit and Research Unit, 2017) described stroke patients attended and transported by LAS. The median response time for suspected stroke patients was 7 minutes. The median on scene time was 32 minutes. 99% of patients were transported directly to a HASU with a median transport journey time of 15 minutes. The median overall call to HASU time was 55 minutes with a slight improvement (median 51 minutes) if stroke was identified on the initial 999 call or a slight delay (median 60 minutes) if stroke was not identified on the initial 999 call. Sheppard et al (Sheppard *et al.*, 2015b) described a median dispatch to hospital time of 42 minutes which was not affected by FAST status or pre-alerting in a UK cohort from the West Midlands.

Introduction of STEAMv2 should have a minimal impact on pre-hospital treatment times unless it changed the destination hospital. Where STEAMv2 introduction could make a difference is pre-alerting.

3.2.9.4 Pre-alerting by paramedics

Pre-alerting has been recognised as a key pre-hospital intervention that impacts on stroke patient outcomes. Pre-alerting by paramedics was independently associated with shorter time to medical assessment for stroke patients in a small Australian study (Mosley *et al.*, 2007). The link between pre-alerting and stroke patient outcomes was expanded upon in a large American study by Lin et al (Lin *et al.*, 2012). Lin et al reported that paramedic pre-alerting of stroke patients was associated with shorter in-hospital times to interventions, such as scanning and thrombolysis, associated with improved patient outcomes.

Abboud et al (Abboud *et al.*, 2016) showed that pre-hospital identification of stroke plus an appropriate pre-alert resulted in a shorter door to CT time than for those patients not recognised as stroke who were not pre-alerted (19 minutes vs 48 minutes). McKinney et al (McKinney *et al.*, 2013) also showed a reduction in in-hospital time to CT scan interpretation (38 vs 48 minutes) and lab results (45 vs 54 minutes) for pre-alerted patients. Oostema et al (Oostema *et al.*, 2014) reported that pre-alerting and high priority transportation were associated with rapid door to CT times. Oostema et al also documented that missed strokes were pre-alerted and transported as a high priority less often. Mckinney et al and Oostema et al both reported a trend towards increased rates of thrombolysis in pre-alerted patients but both studies had small numbers of patients who received thrombolysis so didn't draw firmer conclusions. Hsieh et al (Hsieh *et al.*, 2016) showed that ambulance pre-alerting significantly reduced the door to CT time by 6 minutes and showed a trend towards earlier administration of thrombolysis in a Taiwanese stroke system using CPSS, which is very similar to FAST.

3.2.9.5 Summary of treatment rates and speeds

Pre-hospital stroke care is about rapid recognition of stroke, minimising the time spent in the pre-hospital phase and appropriately pre-alerting the receiving hospital. The introduction of a SM tool may mean that some SM patients would not be pre-alerted or treated with the same urgency as a suspected stroke patient. However, STEAMv2 introduction would potentially reduce the number of SM pre-alerted as stroke which could lead to increased confidence when a stroke pre-alert was placed that it would be a stroke and require urgent attendance. For outcomes related to treatment rates and speeds

introduction of a SM tool has benefits that are difficult to quantify, but which are likely to be small if they exist, and clear risks in terms of delayed access to treatment for stroke patients mistakenly identified as SM.

3.2.9.6 Population disability impact

There are two mechanisms by which pre-hospital stroke care, and identification of SM, could impact on the level of disability in the population. The first is by impacting on time to reperfusion treatment in the form of thrombolysis which reduces disability, which was discussed in the previous section. The second area of impact would be on timely access to specialist stroke units.

Although thrombolysis is a key part of hyper-acute stroke care another very important aspect is rapid access to specialist stroke services which is beneficial for all stroke patients, nor just the minority who are eligible for thrombolysis. A Cochrane review (Stroke Unit Trialists Collaboration, 2013) reported that "*Stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke*". Silvestrelli et al (Silvestrelli *et al.*, 2006) reported that early (<3 hours) admission to a stroke unit improved functional outcomes in a cohort that excluded thrombolysis. Turner et al (Turner *et al.*, 2015) showed that early access to a stroke unit was associated with increased odds of survival over the first year.

Monks et al (Monks *et al.*, 2016) modelled stroke unit capacity and showed that the number of acute beds was linked to delays in accessing the stroke unit for patients. As SM patients account for between 1 in 6 and 1 in 13 HASU beds (Dawson *et al.*, 2016) then reducing bed occupancy by SM should lead to more rapid access for stroke patients and potentially improved outcomes. In summary the introduction of a SM tool should reduce SM use of HASU beds which would allow true stroke patients to be admitted faster. This would be an incremental streamlining of the current process with a small impact on any measure of disability compared to other interventions.

3.2.9.7 Resource implications

The actions attached to a SM tool would define the resource implications for the ambulance service. If SM patients were admitted to a local ED rather than a distant HASU then there may be some savings in terms of distance and time travelled, but there may also be

emergency transfers for stroke patients incorrectly transported to hospitals without stroke units. There may be a reduction in secondary transfers or repatriation of suspected stroke patients who did initially bypass a local hospital to access a distant HASU if some SM were directed to the local hospital. Overall, the numbers of SM patients identified by STEAMv2 are very small, even when applied across a region like the North East as described earlier, and suspected stroke make up only a small proportion of the total calls to the ambulance service so there would be negligible impact on the pre-hospital workforce.

Dawson et al (Dawson *et al.*, 2016) reported the mean length of stay (LOS) in hospital was 2.8 days for SM patients whereas the mean length of stay for a stroke patient was 16.3 days (RCP, 2015). Based on these figures, and the small number of patients identified by STEAMv2, there would be very little if any impact on the stroke services in hospital. Any benefits seen by stroke services in terms of reduced use of resources would be minimal and offset by use of resources elsewhere.

3.2.9.8 Markers of health economic outcomes

Diverting SM patients away from HASUs should be economically beneficial. Admission to HASU is expensive due to the level of care involved, the specialist diagnostics and the multidisciplinary nature of the team. As many SM patients could be appropriately cared for on a non-HASU or general ward there is an economic argument to reduce SM admissions to HASU.

Based on figures from the National Audit Office *(The Comptroller and Auditor General, 2010)* a HASU bed day cost £583, a day on a stroke unit cost £231, whereas a bed day on a general ward cost £181. Using annual inflation figures up to 2017 these costs equate to £744 for a HASU bed day, £293 for a stroke unit bed day and £230 for a general ward bed day.

When Dawson et al (Dawson *et al.*, 2016) reported that the mean LOS on a HASU was 2.8 days for SM patients this figure included two distinct populations. The first comprised 80% of SM patients who were discharged directly from HASU following a mean LOS of 1.7 days. The second population comprised the remaining SM patients who were admitted to hospital and had a mean LOS of 7.3 days. The figures for the patients discharged directly from HASU are similar to those reported by Gargalas et al (Gargalas *et al.*, 2017) for functional SM who

showed that medical and functional SM had slightly different mean LOS on HASU of 2.1 and 1.5 days respectively.

The total cost of a SM patient staying on a HASU, stroke unit or general ward based on the 2017 bed day costs and mean LOS figures from Dawson and Gargalas are shown in table 3.2.3.

Table 3.2.3 Costs for SM stay on HASU, stroke unit and general ward		
Location	**LOS = 1.5 days**	**LOS = 2.8 days**
HASU	£1,116	£2,083
Stroke unit	£440	£820
General ward	£345	£644

The cost saving for admitting a SM to a general ward rather than a HASU ranges from £771 to £1,439 per patient based on these figures. Admitting SM patients to a stroke unit rather than a HASU would save between £676 and £1,263 per patient. However, this assumes that the resources available for stroke care remain constant even though the overall demand for specialist care has fallen because of the avoidance of SM admissions.

Due to the high PPV of STEAMv2 the number of stroke patients who would be incorrectly classified as a SM is very small, but for these stroke patients there would be health economic consequences due to potentially delayed or missed thrombolysis opportunities and ongoing care costs. The SSNAP Health Economics tool for thrombolysis (RCP, 2017c) estimates that missing a single thrombolysis opportunity costs the NHS £3,000 and social care £2,800 over the first year.

Early identification of SM patients could lead to a reduction in the rate of inappropriate thrombolysis. Chapter 1.2 reported that 9% of suspected stroke patients who were thrombolysed were a SM so a simple, cheap intervention like STEAMv2 which could help reduce this rate would have economic benefits. Goyal et al (Goyal *et al.*, 2015) reported on the costs associated with administering thrombolysis to SM patients in the American healthcare system. SM patients who received thrombolysis had an extended length of stay and required higher level monitoring due to the risks associated with thrombolysis. The

overall excess treatment costs for SM patients administered thrombolysis was $5,401 (£3,865) per admission.

Overall, there is a clear health economic argument for reducing SM admissions to HASUs. Reducing inappropriate thrombolysis to SM patients is also desirable from a health economic viewpoint. The potential negative health economic consequences of delayed or missed thrombolysis treatment opportunities are difficult to quantify and will depend on the patient, the severity of the stroke and the ongoing care needs of the patient but could be considerable for a small number of patients.

3.2.9.9 The impact of pre-hospital SM identification on hyper-acute stroke outcomes

When the four outcomes identified by Monks et al were considered there were three distinct groups who would be affected by the introduction of a pre-hospital SM tool: patients, ambulance services and stroke services. The benefits of introducing STEAMv2 were difficult to quantify for patients but there are risks of delayed treatment times or missed thrombolysis. These risks were recognised in the focus groups and interviews described in chapters 2.1 and 2.3. The benefits to the ambulance service are minimal in terms of outcomes related to stroke but may include more efficient use of resources, however any resource benefits would be dictated by local geography and pathways. The benefits to stroke services are clear in terms of economics relating to HASU bed usage but need to be balanced against the impact of missed reperfusion treatment opportunities and the redistribution of patients to other areas of the NHS

3.2.9.10 Strengths and weaknesses

The value of the models described above is limited by their simplicity and the broad assumptions, such as 100% use of STEAMv2, used in their construction and parameter values. The potential consequences were discussed but the outcomes were not linked to the models so variations in pre-hospital stroke and SM recognition could not be directly explored. Sophisticated models which could incorporate multi-site systems and account for the time taken for each decision or action, could be developed using techniques such as discrete event simulation (Monks *et al.*, 2012; Churilov *et al.*, 2013) to provide a more precise estimate of impact of SM identification, but are unlikely to change the overall value.

This work focussed on the suspected stroke population but acknowledges that stroke chameleons needed to be accounted for. Recognition that around 20% of stroke patients are not identified as stroke in pre-hospital care, provides context and information on potential consequences for the small number of stroke patients who may be wrongly classified as SM by a tool like STEAMv2.

Future models which develop in this area could consider the impact of telemedicine and how this would affect the pre-hospital decision making process and whether this would increase the on scene times. Puolakka et al (Puolakka *et al.*, 2016) looked at physician advice via telemedicine and showed that it increased the on scene time so any benefit would need to be carefully considered. The identification of patients suitable for thrombectomy is another issue where the impact of pre-hospital decision making is being considered and the impact of SM on the outcomes is being modelled (Holodinsky *et al.*, 2018).

3.2.10 Conclusions

This exercise resulted in a basic decision tree model that gave a crude estimate of the impact of STEAMv2 in terms of pre-hospital recognition of stroke and SM patients. The simple models used were not able to represent the complexities inherent in multi-site systems of stroke care with varying pathways. The impact of STEAMv2 on the North East region and the UK were considered by simplifying suspected stroke admissions to a single system and making assumptions accounting for the rate of potential bypass. These scenarios were very simplistic and only reported total figures of patients who may be affected by the application of STEAMv2, however they do inform the understanding of potential impact on the stroke care system. The scenarios gave an indication of the small impact that SM identification using STEAMv2 might have, which is unlikely to be changed using more sophisticated modelling approaches such as discrete event simulation. The only outcome area where introduction of a SM tool showed a clear potential benefit was in health economics and this needed to be balanced against the impact of delayed or missed thrombolysis opportunities.

3.2.11 Summary

The impact of pre-hospital SM identification is difficult to quantify but likely to be small using STEAMv2. The complexities of hyper-acute stroke care and the large number of variables in multi-site systems where patients can bypass local hospitals are difficult to model, but this is

where there may a greater argument for a tool like STEAMv2. If stroke services continue to centralise, and more patients bypass local hospitals to access distant HASUs, the low cost associated with STEAMv2 implementation makes it worth considering, assuming that its performance in clinical practice mirrored that suggested by the development, refinement and validation datasets. The results of this chapter were used to inform focus groups with professional stakeholders discussing the development and applicability of STEAMv2 which are described in the next chapter.

Chapter 3.3 Professional stakeholder views on STEAMv2

3.3.1 Introduction

STEAMv1 was refined into STEAMv2 based on an expanded clinical dataset and qualitative data gathered through focus groups (reported in part 2). Chapter 2.2 described the refinements to the STEAMv1 criteria, the addition of FAST-ve and the performance of STEAMv2. This chapter describes the design, data collection and findings of the third phase of qualitative work. This final phase was conducted to explore the views of healthcare professionals about STEAMv2. In addition to paramedics and hospital clinicians from the North East where STEAM was developed, this phase also included paramedics and hospital clinicians from the North West who were not involved in the development process and who worked in a different stroke care system.

3.3.2 Chapter aims

This chapter aims to report the views of healthcare professionals, who have experience and interest in acute stroke care, regarding the structure, development and applicability of STEAMv2.

3.3.3 Methods

The methods used in this phase of the study are identical to those used in the first phase of qualitative research reported in chapter 2.1. The methods are repeated in a shortened form below.

3.3.3.1 Design

A generic qualitative approach (Cooper and Endacott, 2007; Griffiths and Mooney, 2011) was selected. Focus groups were chosen as a suitable method for data collection as they allowed a range of participants, selected for their experience in acute stroke care, to express and discuss their views on the STEAMv2 tool.

3.3.3.2 Participants

Paramedics and hospital clinicians were recruited from two regions, the North East where STEAMv1 and STEAMv2 were developed and the North West, in order to provide a different

viewpoint on the structure, development and applicability of STEAMv2. The North West was also chosen due to the centralisation of stroke services in this region which meant that ambulances bypassed local hospitals to access central HASUs and the use of exclusion criteria by the North West Ambulance Service NHS Trust (NWAS) similar to STEAMv2.

Separate focus groups were organised for the paramedics and the hospital clinicians. This was done in order to focus on the views of each professional group, as opposed to the interaction between the groups, and to avoid any perceived dominance by one group over the other. There was no expectation of reaching data saturation with only two focus groups in each region. The aim was to collect views about STEAMv2, not to report a comprehensive thematic analysis of paramedics' or hospital clinicians' views across the participating organisations.

The four participating organisations in this phase were NEAS and NHCT from the North East and NWAS and Salford Royal NHS Foundation Trust (SRFT) from the North West.

Volunteer sampling was used to recruit participants to focus groups. Participants were recruited by advertising for volunteers within the respective organisations and attendance at existing meetings where relevant professionals were present. All participants were supplied with information sheets regarding the study prior to the focus groups and had a chance to ask questions. Informed written consent was gained at the start of each focus group.

The aim was to recruit 4-6 participants per focus group. These numbers would ensure a variety of views would be represented, with enough participants to promote discussion within a group that would be manageable by a single facilitator.

3.3.3.3 Data collection and analysis

A topic guide was developed with input from the supervisory team for use within the focus groups (see appendix Q). It covered broad areas including the development of STEAMv2 and the results of the modelling work described in chapter 3.2. The guide was intended to help keep the groups focussed on the issue of interest whilst allowing unexpected areas of discussion to arise.

Stimulus material (see appendix R) was used in the form of an overview of the whole project, STEAMv1, STEAMv2 and a summary of the modelling work. This was given to all

participants to stimulate conversation and to act as reference material during the discussions.

Brief field notes were taken during the focus group and used by the researcher to ensure key points were covered and interesting points that arose were investigated without interrupting the flow of conversation.

Digital audio recordings were made of the focus groups. These were transcribed verbatim by the researcher and anonymised for the purpose of analysis. Thematic analysis was conducted using a five stage framework as documented in chapters 2.1 and 2.3.

3.3.3.4 Approvals

Ethical approval for the qualitative phases of the study was gained from Newcastle University Faculty of Medical Sciences Ethics Committee (ref 01203/2016). Health Research Authority (HRA) approval was gained as this project included staff selected due to their positions in the NHS across multiple trusts (ref 207285). This project was adopted onto the National Institute for Health Research (NIHR) Clinical Research Network (CRN) portfolio (ref CPMS 32323). All approvals related to the qualitative work can be found in appendix J.

3.3.4 Findings

Four focus groups were conducted involving 25 participants (eight paramedics, ten doctors and seven stroke nurses). Participants are indicated by codes P1-8, FG3 for the paramedics and H1-17, FG3 for the hospital clinicians. The findings of all four focus groups are presented in one narrative account due to the common topics addressed across the focus groups. Analysis of the transcripts identified 350 concepts which were combined into 31 themes. These were then grouped into five interconnected, over-arching themes: decision making; pre-hospital stroke identification; implementing SM tools within care pathways; strengths and limitations of the STEAM tool; and the stroke mimic population. Decision making was considered to be the core theme which underpinned the other themes. The five over-arching themes are summarised in figure 3.3.1 and described below with anonymised illustrative quotes. The themes reported here are not combined with the themes reported in chapters 2.1 and 2.3 due to the focus having moved from the development of STEAMv1 (chapter 2.1), to usability in the pre-hospital setting (chapter 2.3), to the aim of this chapter which focusses on STEAMv2. There were some common themes which emerged such as decision making/thought processes, the actions that STEAM would lead to and how this type of tool would work across the ambulance to hospital interface.

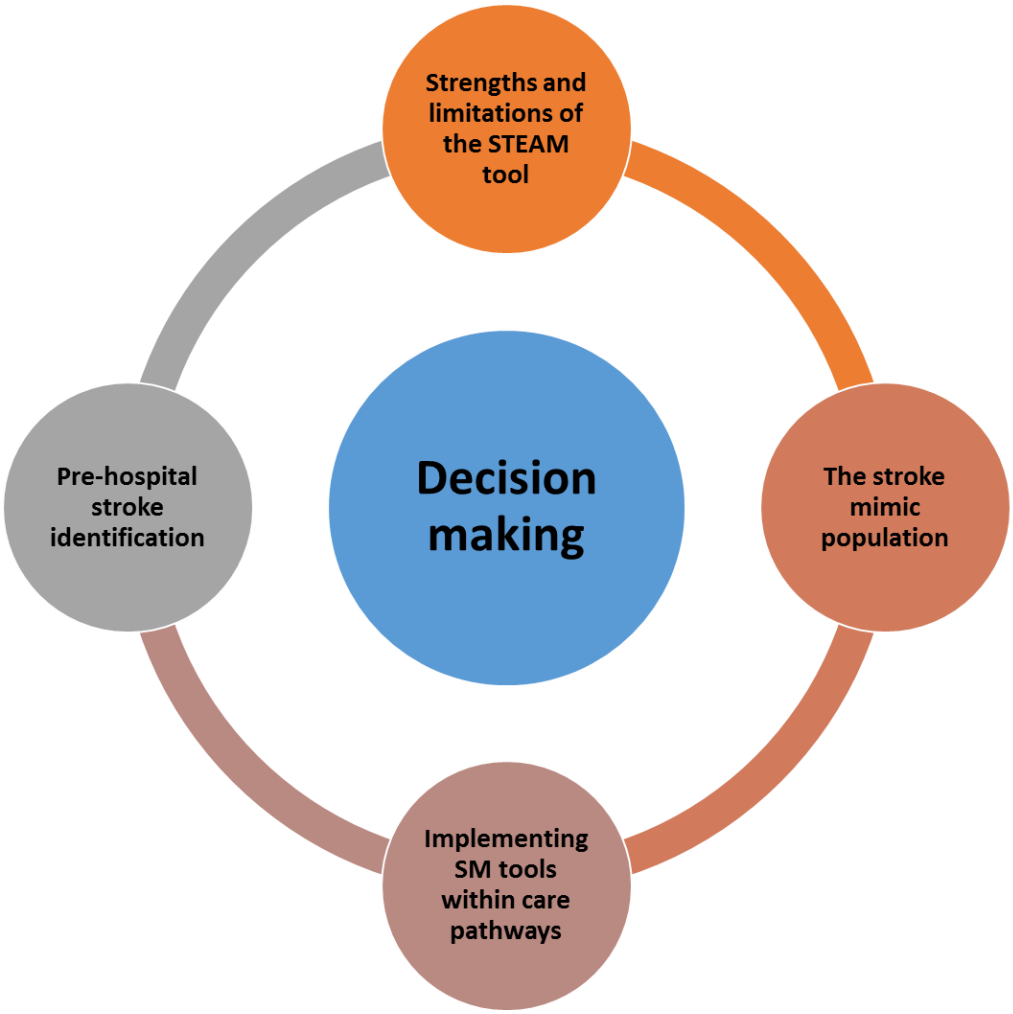


Figure 3.3.1 Themes from the four professional focus groups in phase 3 discussing STEAMv2

3.3.4.1 Strengths and limitations of the STEAM tool

There was general consensus in all four focus groups that STEAMv2 was a pragmatic tool for identifying SM patients and that the development process was methodical and comprehensive:

> *"I think you've undertaken a sensible approach, there's nothing obvious amiss" P4, FG3*

> *"It seems straightforward enough, it's not like it's complicated difficult information to get hold of" N7, FG3*

One point that was raised in the NEAS focus group was that the STEAMv2 criteria should be recorded on any suspected stroke patient, and that STEAMv2 prompted paramedics to question their suspected stroke diagnosis if the observations were unusual:

> *"Some of this should really be common sense shouldn't it, you should be starting to doubt whether this is actually a stroke if you're bringing up these blood pressures, temperatures and heart rates so this it supports really what you're already thinking" P1, FG3*

Participants from NHCT questioned whether STEAMv2 was an improvement over STEAMv1 based on the data from the validation cohort. They also raised concerns about the added complexity of STEAMv2 although the following point was also asserted:

> *"Intuitively looking at the information in the second version it would seem to be better" H7, FG3*

Participants from SRFT preferred STEAMv1 as they did not perceive the increased PPV to be to be a worthwhile trade-off with the reduced sensitivity and increased complexity:

> *"I think you are more likely to get STEAMv1 done in the back of an ambulance than STEAMv2" H15, FG3*

In contrast to the SRFT clinicians the NEAS and NWAS paramedics preferred STEAMv2 but did acknowledge that it was more complex and that some form of memory aide would be helpful:

> *"The only thing about STEAM2 compared to STEAM1 is that you'd probably have to have it on a card just to remember what all of those values are because there's so many parameters in there" P3, FG3*

Paramedic participants commented that the performance characteristics (sensitivity, specificity and PPV) of STEAMv2 were acceptable, and considered specificity to be the most important property:

> *"The important one is that 99% of strokes are being excluded, I think that is the most important of the criteria there" P5, FG3*

Paramedics from NEAS and NWAS asserted that STEAMv2 was preferable based on the increased PPV and were particularly focussed on how it could be applied in practice. Embedding STEAMv2 in electronic patient records was suggested by NEAS who already use electronic records. NWAS paramedics suggested that quick and reliable feedback would be important to increase paramedics' confidence with use of the tool.

However, there were concerns expressed by clinicians in both hospital focus groups about the tangible impact STEAMv2 would have if it was applied in practice:

> *"It probably doesn't make sufficient impact on time, bed numbers or staffing to really make any big, any significant difference" H11, FG3*

There were also concerns raised about who would be responsible if an opportunity to treat a patient was missed due to use of a tool such as STEAMv2:

> *"Is it NWAS that get sued for that, is it the people who made the protocol, is it the DGH* (District General Hospital), *you know, if this is potentially diverting people away from correct treatment who carries the can?" H15, FG3*

The inclusion of age as a criterion, one of the issues raised in the first phase of focus groups reported in chapter 2.1, was once again raised:

> *"I do worry that hidden amongst the 1% who this doesn't pick up are some 30 year olds who have had strokes who if anything need a rather faster response" H11, FG3*

Participants understood why age was included in STEAMv2, but examples of young patients who had strokes were given in two of the focus groups, which emphasised how these unusual cases are prominent in people's minds.

When discussing the linked patient data used to create STEAMv2 it was suggested that future work could consider whether discharge diagnoses were the most appropriate diagnoses to use as the basis for deriving a pre-hospital SM tool. It was suggested that looking for patients who received an early SM diagnosis, or who were not admitted to a stroke unit, might be a more appropriate population to target:

> *"If you took the gold standard to be that the stroke physician was confident enough that they just turned them away then that's what you are interested in, not so much whether the final diagnosis was stroke or not." H14, FG3*

3.3.4.2 The stroke mimic population

Participants in all four focus groups commented on how SM are not a homogenous population:

> *"All mimics are not equal, within them are things that are quite serious and need to be treated quickly and things that don't matter and like you are not going to come from harm coming to a HASU with migraine" H14, Fg3*

One SM condition identified as needing rapid treatment was seizures. The fact that some stroke patients have seizures was explicitly mentioned in three focus groups:

> *"Strokes can cause seizures can't they?" P6, FG3*

Seizures are currently an exclusion criterion in the NEAS and NWAS stroke pathways. All participants seemed comfortable with the idea of these patients being taken to the nearest ED rather than bypassing to a HASU:

> *"The fact that you are trying to pick out sepsis and seizures is good because they could come to harm being carted for many miles past their local ED when they should have been there getting their antibiotics or lorazepam or whatever" H14, FG3*

This highlights that different SM conditions may require different treatments. For some SM conditions such as sepsis the nearest ED is the most appropriate destination as rapidity of treatment is important; whereas for other SM conditions such as brain tumours or functional disorders there are minimal negative consequences for the patient from bypassing their local hospital to get to a distant HASU.

The appropriate pre-hospital treatment for differing SM conditions was discussed and particularly whether SM patients identified by STEAMv2 should be pre-alerted to the receiving hospital. There were differing views on this with North West participants suggesting a different type of pre-alert for SM patients, but the consensus of opinion was that it would be driven by the individual presentation (as some SM patients would need pre-alerting due to their underlying condition):

> *"Some of the stroke mimics can be pretty time critical as well" P2, Fg3*

One participant asked whether STEAMv2 had been considered for use as part of a telephone triage process. This area of application had not been previously considered, but the consensus within the NEAS focus group was that telephone triage should focus on high sensitivity and more refined decision making was only possible when a clinician was physically present with a potential stroke patient.

The potential to use STEAMv2 to trigger a call from a paramedic on scene to a stroke unit for advice was discussed in both North West focus groups. At the time of the focus group NWAS did not have the ability to directly talk to the stroke units, and the feeling from the paramedics was that there was little benefit from being able to do so:

> *"I think if we start having conversations on scene it could be like war and peace and delay our on scene time significantly rather than us just saying we've got this we are coming" P6, FG3*

This view was supported by the hospital clinicians who considered the type of patient where a paramedic might call for advice and what their response might be:

> *"They're going to say well they're not quite moving their left arm but it kind of seems ok, then what are you going to do with that and then it will be stuff like that and you'll just go I kind of have to see them" H14, FG3*

The question of who was responsible for the patient factored into discussions around the risks and benefits of paramedics being able to phone the stroke unit for advice:

> *"The paramedics transferring the risk to the staff here aren't they, and I don't think they would accept that, particularly because they haven't got the patient in front of them" H14, FG3*

Participants from the North West were not surprised by the high SM rate found in the literature or the NEAS data used to develop STEAMv2. Clinicians from SRFT reported their SM rate was still relatively high despite their efforts to reduce the SM rate:

> *"So we are excluding all FAST negatives and we're still getting a 25% mimic rate" H15, FG3*

3.3.4.3 Pre-hospital stroke identification

How stroke is identified in the pre-hospital setting was a theme that emerged primarily from the two focus groups with ambulance services.

The FAST test is the main stroke identification criteria, used by both NEAS and NWAS, in their stroke pathways:

> *"It's very black and white, they're either FAST positive or FAST negative, FAST positive stroke going to HASU, FAST negative they're not" P3, FG3*

> *"We are very blunt at the minute as I say it's FAST positive or negative and nothing in between" P8, FG3*

FAST negative patients were particularly problematic for the paramedics. They perceived that hospitals were reluctant to accept referrals for FAST negative suspected stroke patients. In the North West the volume of patients admitted to the HASUs was considered to be a factor by the paramedics:

> *"In terms of resources they can't just take everything suspected, its got to be quite clear cut for them and in terms of numbers they get through the door I just think it's why they can be quite sort of it's not FAST positive we can't take it" P8, FG3*

The clinicians in the North West commented on the volume of patients they received due to the centralisation of services, and also mentioned that the exclusion of FAST negative patients by NWAS was not in agreement with national guidelines:

> *"They* (the Royal College of Physicians Stroke Guideline) *do say that if they suspect a stroke they should bring them, which I think is what they do in practice" H14, FG3*

Several paramedics were confident in their ability to identify stroke patients despite the evidence around the SM rate, and knowledge about the limitations of the FAST test:

> *"Sometimes you turn up and it's blatantly obvious that it's a stroke" P1, FG3*

Other paramedics were aware of how their impression formed the initial part of the stroke identification chain:

> *"We are not saying they have had a stroke, we are saying they are FAST positive, that's why we brought them here so you can scan them and find out more" P6, FG3*

There was recognition in all four focus groups that SM were an inevitable part of the existing model of stroke care, and that a balance between sensitivity and specificity of pre-hospital stroke identification was necessary:

> *"I don't know if there is an answer, I don't think there is, I think it's just one of those things that perhaps has to happen, that we get the mimics so what we make sure we do get all the patients and for paramedics not to feel like they've missed a patient" H17, FG3*

3.3.4.4 Implementing SM tools within care pathways

The stroke care pathways which connected the ambulance services with the receiving hospitals in both regions were a prominent theme in the focus groups. The paramedics described how their stroke pathways were very prescriptive and largely dictated by FAST:

> *"You sort of think these things to yourself when you've got a FAST positive patient but you think we've got this tool to follow, we can't deviate from it" P6, FG3*

> *"We've bred people, everybody to go they're FAST positive they're having a stroke" P4, FG3*

Once the paramedics had identified a suspected stroke patient the pathway then became more variable due to local hospital practices:

> *"It changes so much between hospitals and areas" P8, FG3*

The organisation of stroke services within the hospital influenced the extent that participants thought a pre-hospital SM identification tool would beneficial:

> *"Another consideration would be say if you were going to the same hospital anyway, so if your local ED happened to be where your HASU was you wouldn't be concerned but if you were going somewhere, a hospital, like a district general that doesn't have a HASU then people would be a bit more nervous" P6, FG3*

> *"If I were a stroke consultant working at* (a local district general hospital) *then it would seem reasonable for people who were scoring on this type of thing to go to ED rather than coming direct to the stroke unit cause the chances are very very high that they don't need stroke unit input" H11, FG2*

Clinicians in the North West were of the view that paramedic perceptions of the best hospital for the patient, along with a culture of treating for the worst possible outcome, would make implementation of a SM tool difficult. They considered that paramedics would take suspected stroke patients to a HASU regardless of what a SM tool indicated:

> *"Because we've got this centralised service we're also the neuro centre so I think they think so what if it's a mimic, this is the neuro centre so it's the best place for them anyway" H14, FG3*

Paramedics and hospital clinicians recognised that there were consequences of bypassing all suspected stroke patients into a HASU:

> *"If you take somebody who is FAST positive to a HASU, and you've bypassed the nearest ED, they go to HASU, they have a scan, it's not a stroke, they've then got to be repatriated back to the local ED so it's more money for the ambulance service, the hospital, it's bad for the patients, its poor experience for them" P6, FG3*

> *"We're seeing loads of mimics when these people really don't need to be here and its an ongoing problem, it's not fair on the patients that they and their family then have an hours journey the next day to come for visiting time because the other problem with the mimics is we don't have a repatriation policy" H15, FG3*

Issues with repatriation are influenced by local geography and pathways. This was highlighted when the North West HASU model was compared with London:

> *"In London where everyone is within 20 minutes of a HASU it's not such a big issue cause you'll only be 20 minutes from your home wherever you go" H15, FG3*

The North West differs from the North East, and most other regions in the UK, in that NWAS has extensive pre-hospital exclusions that direct paramedics to take patients to local hospitals rather than HASUs. Most UK ambulance services identify suspected stroke patients based on FAST, exclude hypoglycaemia and seizures, and patients who aren't excluded based on these two factors are taken to a HASU or stroke unit. The NWAS exclusion criteria are similar in nature to STEAMv2 and are listed below:

- Age<16 years
- Airway compromised following basic manoeuvres

- Respiratory rate<10 or >30
- SaO2<90% post high flow O2
- SBP<90mmHg
- Heart rate<40 or >150
- GCS<8
- Any seizure activity reported during or causing this incident or 999 call
- BM<4.0mmol/l post treatment

The impression from the North West clinicians was that their exclusion criteria already filtered out a significant proportion of SM:

> *"I don't think this would add anything to our current setup, I know we've got quite, a fairly robust system in place already" H15, FG3*

This view was tempered by questions over how the existing North West exclusion criteria had been developed and how they were perceived compared with how the possible application of STEAMv2 was being perceived:

> *"It's interesting isn't it that our criteria were just introduced, well I don't know if we've ever been able to work out where they came from or who made them up but they've just been introduced, whereas you know you've very carefully tested these criteria and thinking about it and there's a huge kind of disconnect where we've just gone ahead and done that and that's fine whereas you've now got data and everybody's going oh I don't know about this" H14, FG3*

The performance of the North West exclusion criteria is compared with STEAMv2 in the discussion section.

3.3.4.5 Decision making

Decision making was the core theme as it featured strongly within the other themes. Decisions about how STEAMv2 should be applied, decisions about which SM could be appropriately treated at a local ED and who should make that decision, including the impact of how paramedics decide a patient is having a stroke and what subsequent decisions are available within existing pathways emerged within all the focus groups

One point which encapsulated the themes discussed so far was the idea of railroading or diagnostic momentum (Satya-Murti and Lockhart, 2015). This is where a decision sets a chain of events in motion that are difficult to deviate from. For stroke care, a tool like STEAMv2 could alter the normal chain of events:

> *"The crew get there and go oh they're having a stroke and it's way down the line before someone goes, actually after they've been and come back from scan, they haven't, whilst if you use this you might go yeah they're probably not having a stroke just take them to ED" P3, FG2*

This idea of railroading overlaps with who takes responsibility for making the decision that a patient with stroke-like symptoms is actually a SM and how this fits into local pathways. The paramedics viewed STEAMv2 as a tool which would support their decision making and allow them to make informed decisions rather than following simple protocols based on the patient being FAST positive or negative:

> *"You are making these judgments all the time, you are talking to people and then trying to say do I think this is a stroke, do I not think this is a stroke" P3, FG3*

Paramedics recognised that it is very difficult to design a tool that covers all the possibilities encountered in medicine, but they recognised the potential for STEAMv2 to improve their decision making:

> *"It will be a tool to support your decision making, it won't be the be all and end all" P2, FG3*

The need to justify decisions and defend how those decisions were made underpinned concerns about being challenged for adopting something like STEAMv2 that represented a change from the current protocol:

> *"A lot of our job comes down to justification doesn't it, so long as you've got something to back up why you've done or not done something then people are more likely to embrace it and feel confident doing it" P6, FG3*

One of the paramedics gave an example of a decision support tool (Newton *et al.*, 2014) that had been implemented to help them to identify patients suitable for treatment in the community or at locations other than ED:

"Pathfinder is a good example of how you support staff who aren't necessarily confident in their decision making, Pathfinder works because people then have a very clear process to follow and that they can fall back on and say that I followed that and that's what happens" P4, FG3

This demonstrated that when paramedics were supported in their decision making and had clear pathways to follow, then decision support tools were both feasible and acceptable to use in practice.

3.3.5 Discussion

This final phase of qualitative work reports the views of paramedics and hospital clinicians regarding the structure, development and applicability of STEAMv2. This generated five prominent themes: strengths and limitations of the STEAMv2 tool which recognised the simplicity and specificity of STEAMv2 but also the potential for false positive stroke patients; the SM population which included the heterogeneity within the population and considered what constituted appropriate treatment; pre-hospital stroke identification which highlighted the importance of FAST and the inevitability of SM; implementing SM tools within care pathways recognised local and regional differences; and decision making included who should make the decision and what support they might need.

Decision making factors were key themes that featured strongly in this chapter as well as chapters 2.1 and 2.3. For a paramedic to decide that a patient with stroke-like symptoms was a SM and to then treat that patient as a SM would be an important decision and represent a substantial change from current practice. Paramedics and hospital clinicians were acutely aware of the potential risks (delayed or missed thrombolysis) and benefits (reducing SM bypass of local ED to access distant HASU) of making this decision.

The views expressed by the paramedics were similar across the two regions with a high degree of acceptance of STEAMv2, the need for justification and support for appropriate decision making along with recognition of the influence of local pathways. The hospital clinicians also shared similar views across the two regions with regards to concerns about age as a criterion and missed opportunities to treat stroke patients. Hospital clinicians in both regions stated that STEAMv2 had potential benefits, particularly with future implementation of thrombectomy services and potential large-scale bypass to neurosurgical

units. However, neither group considered that STEAMv2 would improve their current system; despite there being marked differences between the pre-hospital pathways in each region.

Participants saw potential value in a tool like STEAMv2 in a system with more bypass of local EDs and longer transfer times. If STEAMv2 were to be implemented in this type of system there was a lack of agreement between SRFT and NHCT as to whether STEAMv1 or STEAMv2 was the optimal structure. Regional differences would make implementing STEAMv2 on a large scale and studying any impact challenging. Overall participants thought that pre-hospital SM identification was logical and that STEAMv2 had been developed in a robust way, but due to the lack of tangible benefits and concerns around young stroke patients it did not represent an improvement over current systems.

The perception of SM as a heterogeneous group was a topic that featured prominently in this phase. STEAMv2 was developed on the hypothesis that SM do not need to be treated at a HASU. The key messages from participants were that some SM patients would benefit from earlier treatment at a local ED and may be harmed by extended bypass; whereas for some patients it probably makes a negligible difference.

The criteria used by NWAS to exclude suspected stroke patients from their stroke pathway were a topic of discussion in both North West focus groups. STEAMv2 and the NWAS exclusions share some common elements: hypotension, heart rate and seizures. The NWAS pathway was perceived as more acceptable than STEAMv2 despite lacking a robust development process and evidence of benefit. The performance of the NWAS exclusions are explored further below.

The potential use of telemedicine and the ability for paramedics to directly contact stroke units was highlighted in this phase of the research. Three focus groups concluded that a SM decision would be optimally made in the pre-hospital setting, and that telemedicine offered little benefit and could potentially delay the decision-making process. NHCT explored the potential to use telemedicine to inform the pre-hospital decision making and considered how STEAMv2 could be applied in other settings such as ED triage.

Participants' views about the results of the modelling have not been presented as a separate theme but are included within the other themes. The small numbers of patients who would

be impacted, based on the modelling outputs, influenced participants' perceptions of the lack of tangible benefit that introducing STEAMv2 would have. The four impact areas (treatment rates and speeds, population disability impact, resource implications, health economics) considered in the modelling were all discussed and contributed to the findings presented. The risk of delayed thrombolysis and missed opportunities to potentially reduce disability was of concern to participants, the workforce impact would mostly be seen in the ambulance service, and the economic benefits of reducing SM admissions to HASU needs to be balanced against the potential missed thrombolysis patients.

3.3.5.1 Comparing STEAMv2 with the NWAS exclusions

During the focus groups the NWAS stroke pathway were repeatedly referred to. NWAS participants remarked on the similarity between the STEAMv2 criteria and the NWAS stroke pathway exclusions. One SRFT participant commented on how they didn't believe STEAMv2 added anything to their existing pathway, but another participant identified that their current criteria had not been developed or tested in a robust fashion.

In order to address these comments, the NWAS exclusions were tested on the complete North East dataset (refinement and validation cohorts combined). This complete dataset included 5,645 patients with 3,483 (62%) stroke patients and 2,162 (38%) SM patients. The results of testing the North West exclusions in this dataset are shown in table 3.3.1.

Table 3.3.1 NWAS exclusion criteria tested in complete North East dataset

Criteria	**Patients**	**Stroke (%)**	**SM (%)**
FAST-ve*	421	196 (47)	225 (53)
RR<10	0	0	0
RR>30	37	18 (49)	19 (51)
SpO2<90	121	69 (57)	52 (43)
SBP<90mmHg	13	7 (54)	6 (46)
HR<40	4	0 (0)	4 (100)
HR>150	25	16 (64)	9 (36)
Seizures	148	30 (20)	118 (80)
BM<4.0	26	10 (38)	16 (62)
Total**	**763**	**333*** (44)**	**430 (56)**

* FAST-ve patients were removed initially, other criteria are reported on FAST+ve patients

** Total values represent patients with any exclusion criterion so columns will not add up

***333 stroke patients included 36 TIA patients

There are a number of limitations to this testing:

- NWAS excludes under 16, NEAS data based on 18+.
- Unable to report on compromised airway patients.
- NEAS physiological data represents mean values across the patient encounter.
- Unable to comment on administration of high flow O2 for the SpO2 value.
- GCS<8 patients were excluded from the NEAS data.

With these acknowledged limitations, the results of applying the NWAS criteria and STEAMv2 to the complete North East dataset are reported in table 3.3.2.

Table 3.3.2 Comparison of NWAS exclusion criteria and STEAMv2 in complete North East dataset

Patients identified	NWAS exclusions	STEAMv2
Suspected stroke	763 (14%)	133 (2%)
Stroke	333 (10%)	14 (0.4%)
SM	430 (20%)	119 (6%)

NWAS is the only UK ambulance trust with extensive stroke pathway exclusions similar to STEAMv2 (see appendix S which is discussed more in chapter 4.0). Comparing these in the same dataset revealed that the NWAS exclusions identified nearly as many strokes as SM patients whereas STEAMv2 identified far fewer stroke patients. Replacing the NWAS criteria with STEAMv2 would result in a substantial increase in the total number of patients taken to the North West HASUs.

3.3.5.2 Strengths and limitations

The inclusion of views from paramedics and clinicians across two regions is a clear strength and highlights how local pathways and the interactions between paramedics and local hospitals need to be considered when developing pre-hospital interventions.

The themes presented here compliment and expand upon those presented in chapters 2.1 and 2.3. Chapter 2.1 described the initial views of paramedics and clinicians about STEAMv1 and the development process and identified areas such as age and BM that were addressed in the refinement process. The importance of decision making was also recognised at this early stage and it emerged as a central theme in the subsequent qualitative phases. Chapter 2.3 explored the applicability and usability from the paramedics' perspective and expanded on how STEAM could be applied in the pre-hospital setting and how it could influence decision making. This topic was further explored in this chapter with some similar opinions expressed by the NWAS paramedics.

It could be inferred that the small number of sites involved, and participants' experiences based on local and regional pathways are not representative of the wider professional groups. However, representing the views of all paramedics or stroke clinicians was not the aim of this phase.

3.3.5.3 Future research

The focus groups supplied useful suggestions for areas of future research such as targeting patients who were identified as SM early on rather than using discharge diagnoses, considering activity over a larger geographical area and how thrombectomy services would interact with a tool like STEAMv2.

Future qualitative work in this area would benefit from the inclusion of the patients' viewpoint which is not represented here. This would be important to consider as patients may have preferences as to where they are treated which would need to be taken into account. Also, decisions about what performance characteristics are acceptable, with the inevitable trade-off between sensitivity and specificity, would also benefit from patient input. The impact of thrombectomy services and how many SM patients potentially travel even longer distances would be another area to seek views on.

NWAS have different types of pre-alerts depending on how the patient presents and future work in this area could consider whether a more nuanced version of STEAMv2 could be used to identify different types of SM that require different responses.

3.3.6 Conclusions

Paramedics' and hospital clinicians' views about STEAMv2 were that it had been developed in a methodically acceptable way and had strong face validity. Concerns about the age criterion echoed concerns raised in earlier phases of qualitative work, despite the changes to the STEAM scoring criteria. Participants' views were mixed on whether introducing STEAMv2 would produce a tangible benefit for patients or local services. If a SM tool were to be introduced, then using telemedicine to inform the pre-hospital decision making was perceived to add little benefit. Factors such as existing local and regional pathways, paramedics perceptions of appropriate treatment and destinations, whether a SM tool would produce any tangible benefits and the impact of current practices on SM patients would all need to be considered further if STEAMv2 were to be implemented.

3.3.7 Summary

The findings reported in this chapter build upon the findings of chapters 2.1 and 2.3 and represent the views of paramedics and hospital clinicians on the structure, development and applicability of STEAMv2. These focus groups generated information on facilitators and barriers to implementing STEAMv2 into clinical practice. The barriers identified emphasise the importance of consultation work to explore how to optimally integrate a tool like STEAMv2 within pre-hospital to hospital pathways. Participants thought SM identification had potential benefits but that these would be dependent on the local systems and pathways.

Chapter 4.0 Discussion and conclusions

4.0.1 The development of STEAMv2

This thesis includes a series of interconnected projects that build upon each other in order to develop and evaluate a pre-hospital SM identification tool. The overall study is aligned with the 'development' and 'Feasibility and piloting' stages of the MRC framework for the development of complex interventions with the qualitative sections informing how STEAMv2 could move into the 'Evaluation' and 'Implementation' stages (Craig *et al.*, 2008). The need to explore this issue was evident as the systematic review (chapter 1.2) reported that 26% of pre-hospital suspected stroke patients were SM. The findings of chapter 1.4 revealed a higher SM rate (41%) in the NEAS population which highlighted the scale of the problem in the North East. The systematic review illustrated the frequency and variety of SM conditions and pointed towards how difficult it would be to identify SM conditions in pre-hospital care.

The SM tool development (chapter 1.5), refinement (chapter 2.2) and validation (chapter 3.1) stages constitute the core of the thesis and followed the methods laid out in a series of papers published in the BMJ in 2009 (Altman *et al.*, 2009; Moons *et al.*, 2009a; Moons *et al.*, 2009b; Royston *et al.*, 2009). The development process was underpinned by the data analysis but was also clinically driven to create a simple and specific tool for pre-hospital SM identification.

Linkage of the NEAS data to the patient diagnoses supplied by the hospitals was a key factor in the success of this project. Linkage with individual hospital trust data was time consuming and resource intensive, but provided richer data than would have been achieved if aggregate regional or national data had been used.

Existing SM tools have not reported qualitative input in their development. In this thesis qualitative work with professional stakeholders, reported in chapters 1.3, 2.1, 2.3 and 3.3, guided the development of STEAM and STEAMv2. This work revealed contrasting views from paramedics and hospital clinicians in terms of whether STEAMv2 was acceptable or which version of STEAM was preferable. Participants thought that STEAMv2 would not be a significant improvement to existing systems, despite agreeing that the number of SM admitted to stroke services was an issue. The different views expressed by the paramedics

and the hospital clinicians may reflect the differing frames of reference of the two groups i.e. short term emergency versus longer term complete pathway. The stakeholder input informed the understanding of the problems with SM identification and the increasing realisation throughout the project that the tool that was developed may not be clinically acceptable.

The multiple methods described in this thesis have created a SM identification tool based on a large sample of retrospective data with a development process that incorporated stakeholder views at multiple points. This multi-methods approach has produced STEAMv2, a robustly developed and validated tool with credible qualitative data providing insights into potential facilitators and barriers to future implementation.

4.0.2 Other SM tools

Ten previous SM tools were described in chapter 1.1. None were developed on pre-hospital data or intended for pre-hospital use. STEAMv2 includes elements that appear in many of these existing tools (age, seizures, migraine, SBP). The existing tools have been reported using a variety of measures but the ones that report sensitivity and specificity appear to favour specificity. Two of the best performing tools included elements that are not routinely available in current pre-hospital practice (NIHSS, (Ali *et al.*, 2014); CTA, (Chang *et al.*, 2012)).

None of the existing SM tools included BM as a predictive characteristic, although ROSIER (Nor *et al.*, 2005) had BM<3.5mmol/l as an exclusion criteria which influenced its inclusion in STEAMv2. There were very small numbers of SM patients with hypoglycaemia in the data so improving pre-hospital identification of diabetic SM may be more about reinforcing existing training and practices.

The tool developed by Tobin et al (Tobin *et al.*, 2009) had similar performance characteristics to STEAMv2 (sensitivity 7%, specificity 99%). Tobin et al concluded that most of the SM patients in their cohort required or benefitted from neurologist input and judged that their tool was not clinically useful. STEAMv2 was developed in a setting with a higher SM rate (40% vs 22%), identified patients who potentially would not require immediate neurological input (sepsis, syncope) and for a more clearly defined purpose in terms of reducing unnecessary bypass of local EDs, so despite the similarities in performance may still have some clinical value.

STEAMv2 was developed using similar methods to existing tools but for application in a different setting. Common predictors of SM diagnosis were identified in the pre-hospital data that were identified by other tools and datasets. The qualitative data presented in this thesis adds information about the applicability and barriers and facilitators to use of a SM tool.

4.0.3 Strengths and weaknesses

The work in this thesis followed a clear development process to iteratively develop a SM identification tool with a clearly defined purpose guided by the principles of simplicity and specificity. This process produced a tool with high content validity due to the professional stakeholder input.

The large sample size and detailed pre-hospital data, including narrative data, gives confidence in the validity of the tool created. The only paper describing a larger sample of SM patients is the work by Merino et al (Merino *et al.*, 2013) which described 8,187 patients from North America. They described a higher than average SM rate (30%) and found that younger age, female gender and characteristics such as absence of hypertension were all associated with SM diagnosis, which is consistent with the findings in this thesis.

One limitation of the methods used was the use of deterministic and probabilistic methods for data linkage which resulted in assumptions being made about the diagnoses of a small number of patients. A further limitation is the incompleteness of the retrospective data which reflected the uncontrolled clinical recording of variables of interest. Prospective data collection would have been optimal and potentially may have produced different results. One area where data wasn't gathered from the pre-hospital records was time since onset. The absence of this data is a weakness of this study as this data would have allowed patients within the thrombolysis time window to be identified and explored as a subgroup of interest.

The professional stakeholder input at multiple points during the development process was a strength of the project and enhanced the applicability of the tool. The qualitative data informed the development of STEAMv2, generated insights and ideas for other projects (such as the exploration of the North West pathway exclusions in chapter 3.3) but also raised

the issue of whether it was acceptable for paramedics to identify a patient as a SM, even with the high levels of specificity that were aimed for.

The lack of patient input into the development of STEAMv2 is a further limitation. Now STEAMv2 has been developed and validated, future work could involve presenting it to patients and carer groups in order to gain their perspective on its potential impact. Their insights would be invaluable when considering the acceptability of potential changes to existing regional or multi-system pathways.

4.0.4 UK Pre-hospital stroke care

This project was based on suspected stroke patient data collected in the North East and it was assumed that the North East was representative of the UK. Geographical variability in pre-hospital stroke care was identified as a factor to consider from the survey of paramedics (chapter 1.3). Discussions with paramedics and clinicians in the North East and the North West (chapter 3.3) revealed differences in their respective stroke pathways. As the pre-hospital stroke pathways provide the context for any discussion of STEAMv2 application, a survey of UK pre-hospital stroke care pathways was conducted so that STEAMv2 could be considered with an up to date view of national pre-hospital practice. The results are in appendix S.

This survey of UK ambulance services showed that pre-hospital stroke pathways generally reflected national recommendations. FAST was the standard stroke identification tool and seizures and reduced GCS were the most common exclusions. Pathways that included elements beyond FAST appear to be focussed on increasing the sensitivity of pre-hospital stroke identification by adding additional symptoms such as loss of balance or vertigo rather than increasing the specificity and PPV. This increases the relevance of a SM identification tool. Only one service had exclusion criteria similar to STEAMv2, therefore a SM identification tool would be novel for the majority of UK ambulance services.

4.0.5 Implementation of STEAMv2

The training necessary for implementing STEAMv2 appears to be minimal based on the usability testing in chapter 2.3. Implementation of any SM tool would need to involve multiple parties including the ambulance service, ED and hospital stroke services.

Implementation of STEAMv2 would need to consider interactions with the current stroke pathways and the sharing of responsibility for patients with negative consequences.

STEAMv2 could be implemented as it is cheap, easy to train paramedics to use and should reduce the use of stroke services resources by SM. However, the lack of tangible impact and the potential for a small number of patients to have delayed access to treatment means that STEAMv2 was not seen as beneficial in the context of current pre-hospital and hyper acute stroke systems. The potential risks to individuals were perceived as outweighing the potential service level benefits.

STEAMv2 could be implemented as part of a pre-hospital stroke care pathway using an algorithm type decision support tool. Clinical algorithms are commonly used in pre-hospital care to describe actions that should be taken in particular circumstances. The UK national ambulance guidelines use algorithms to represent the appropriate actions in situations including cardiac arrest, termination of resuscitation and foreign body airway obstruction (Association of Ambulance Chief Executives and Joint Royal Colleges Ambulance Liaison Committee, 2016). An example of what this might look like for STEAMv2, based on current thrombolysis timeframes and algorithms used in NEAS and other UK ambulance services, is shown in figure 4.0.1. Criteria such as the 4.5 hours since onset which is based on current ambulance practice could change due to thrombectomy service introduction. The final actions based on SM identification were key issues that were consistently identified during the qualitative phases of this study with participants debating what actions were appropriate. The exact criteria would be determined by the local ambulance and stroke services based on their geography and existing regional pathways.

A potential method of supporting implementation of STEAMv2 into pre-hospital practice would be through an electronic platform or an app for use on a smart phone. An electronic tool was supported in the survey (chapter 1.3) and the qualitative work (chapters 2.1 and 2.3). Stroke related pre-hospital electronic decision tools have been developed in recent years (Connected Health Cities, 2018). The algorithms underpinning these electronic tools are fairly simple once the tool itself is developed, they can be used to collect large amounts of data and can be updated remotely. However, there are information governance, IT integration, data security and technological support issues which would need to be addressed if they were to be used on patients. Porter et al described some of the issues with

introducing a computerised decision support tool into pre-hospital care and highlighted the need for organisational support (Porter *et al.*, 2018). Support from multiple organisations including ambulance and receiving trusts, would be needed if a tool such as STEAMv2 were to be introduced in order to give staff the confidence to apply it in practice.

Pre-hospital stroke algorithm

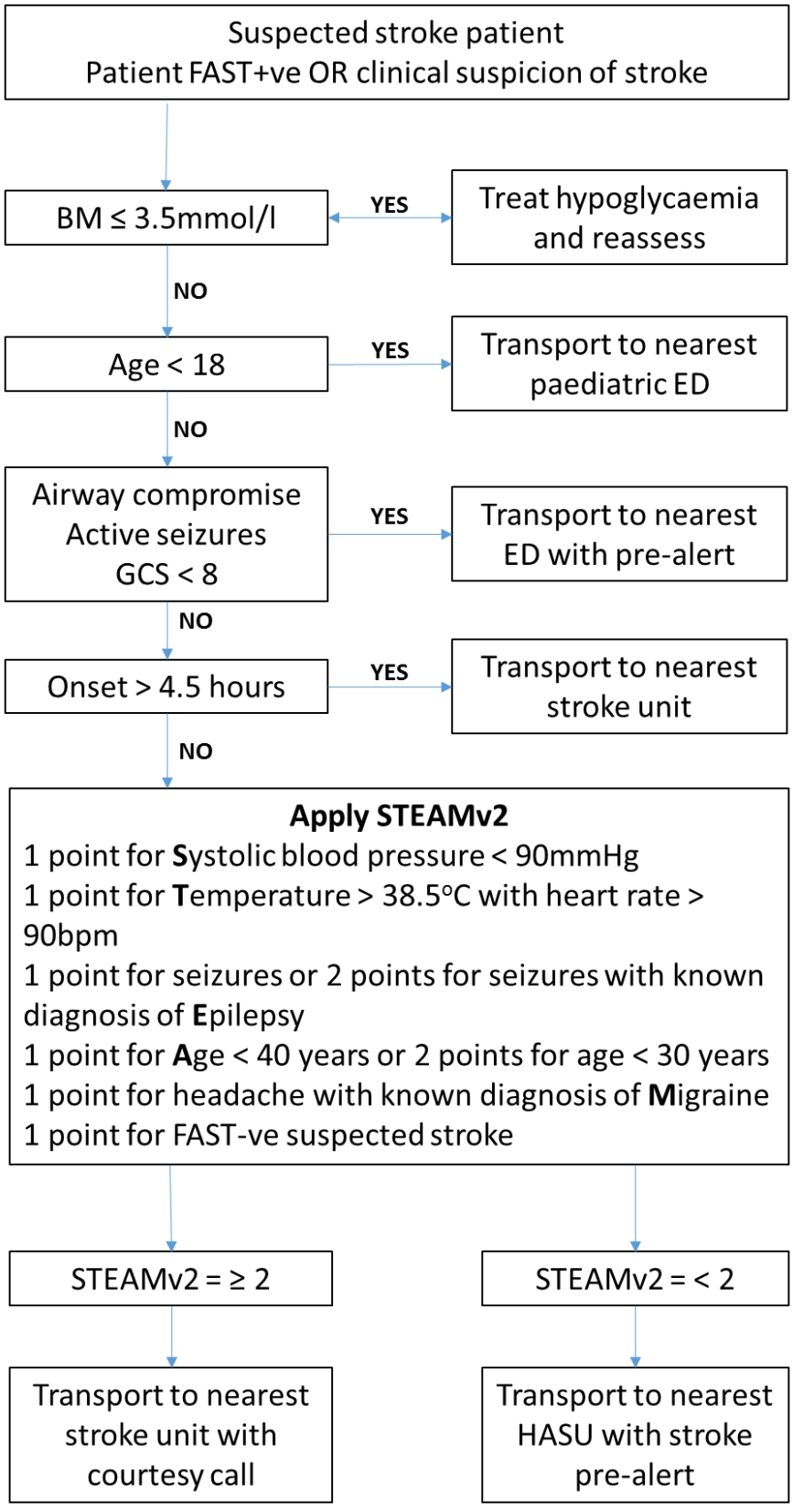


Figure 4.0.1 Potential pre-hospital stroke algorithm integrating STEAMv2

If STEAMv2 were to be implemented then further research would be needed to evaluate its impact in practice. The research designs suitable for evaluating the impact of this type of decision tool include a randomised controlled trial (RCT), a stepped-wedge design or an interrupted time series (Moons *et al.*, 2009a)(Moons *et al.*, 2009a)(Moons *et al.*, 2009a)(Moons *et al.*, 2009a)(Moons *et al.*, 2009a)(Moons *et al.*, 2009a). An RCT could involve cluster randomisation, which is frequently used in pre-hospital research (Mason *et al.*, 2007; Perkins *et al.*, 2015), of ambulance stations where intervention paramedics use STEAMv2 and the control paramedics continue with standard care. Information would need to be collected and recorded in a standard fashion and ideally all patients admitted to hospital would need similar assessments. Outcomes would focus on the rate of correct diagnoses, process measures such as rate and time to thrombolysis and ultimately an evaluation of impact on patient health outcomes. There would be ethical issues with how and when patients would be consented to be included in the study and potential issues around STEAMv2 false positives having delayed access to treatment which would need to be addressed.

This thesis focussed on decision making by paramedics in the pre-hospital setting but the idea of a SM identification tool has potential applications beyond this setting. During the study there were discussions about use of STEAM for telephone triage or in primary care. Telephone triage is not a good target for attempting to identify a patient as a SM using STEAMv2 as any decision about potential stroke symptoms ideally requires face to face contact and a clinical assessment of the patient. STEAM and STEAMv2, and the information used to develop the tools, were also of interest to clinicians working in primary care as they see suspected stroke patients in the community similar to paramedics.

Authors of other SM identification tools such as the FABS (Goyal *et al.*, 2016b) have discussed how they could be used to select patients for advanced imaging in hospital to aid in identifying patients who are less likely to have had a stroke. Dawson et al (Dawson *et al.*, 2016) also discussed the use of risk stratification to identify patients that would benefit from early advanced imaging who could then be discharged from the HASU. STEAMv2 could also be used for a similar purpose, although when the patient is in hospital with access to a wider range of tests and specialist input, factors such as appearances of initial CT brain imaging could be considered for making the SM decision.

4.0.6 Future implications of SM identification

Since this project was first envisaged, stroke and pre-hospital care has advanced. Stroke services continue to evolve in order to deliver the highest standard of care to stroke patients. Developments in hospital based stroke care will drive changes in pre-hospital stroke care, e.g. thrombectomy services may require new bypass models, but pre-hospital developments may also influence hospital stroke care, e.g. portable ultrasound and telemedicine allowing paramedics to assess patients and transmit images to remote neurologists. In all of these developments, and any research around improving stroke care, identifying and targeting the correct patients will be vital to showing the benefit, so detection and exclusion of SM will continue to be of interest.

Thrombectomy services are being commissioned and regional pathways to access these services are being planned (Evans *et al.*, 2017). The implementation of thrombectomy services will focus attention on improving the identification of stroke patients, in order to avoid transferring SM patients long distances to regional providers. Purrucker et al (Purrucker *et al.*, 2017) designed a combined scale to identify stroke, grade severity and detect LVO which is unusual in that it is a single tool rather than sequential use of multiple tools. Although various models of implementation are being discussed, primarily mothership versus drip-and-ship (Evans *et al.*, 2017; Milne *et al.*, 2017), all thrombectomy services will be more efficient if SM patients are correctly identified. The rate and impact of SM patients "incorrectly" taken to thrombectomy centres will need to be considered to optimise the efficiency and cost effectiveness of these specialist regional neuroscience centres.

Stroke services continue to centralise at fewer, larger HASUs (Allen *et al.*, 2017). This will increase the burden of SM on these large HASUs and may lead to more interest in reducing the SM rate by improving pre-hospital stroke identification. There is no new investment anticipated for pre-hospital stroke care specifically, and a simple, cheap assessment may be attractive even if the impact is small at a local level.

Mobile stroke units continue to gain traction, particularly in the USA. The first unit in the UK was being trialled in Southend in April 2018 (Southend University Hospital, 2018). Mobile stroke units may be able to identify some SM in the pre-hospital setting and avoid HASU

admission, but this would be a very expensive way of addressing this issue. There is also a growing interest in novel diagnostic technologies for improving pre-hospital stroke identification which are discussed below.

4.0.7 Diagnostics

STEAMv2 is an attempt to improve the diagnostic performance of paramedics using data that is currently available in the pre-hospital setting. However, there are a number of studies looking into new methods of identifying and more accurately diagnosing stroke which may impact on pre-hospital pathways.

Blood based biomarkers have the potential to improve acute stroke diagnosis (Whiteley *et al.*, 2012; Restrepo *et al.*, 2016; Bustamante *et al.*, 2017). Taking blood in the prehospital setting is possible and could aid stroke and SM diagnosis (Mattila *et al.*, 2016). Biomarkers have not been introduced due to a lack of evidence of performance in real world settings, but they do have the potential to help with identifying stroke, differentiating types of stroke and excluding SM. They could be used in conjunction, or in sequence, with currently used tools such as FAST to improve the sensitivity and specificity of stroke diagnosis or STEAMv2 to improve the accuracy of SM diagnosis. One study that is currently under development is the PRISM study (UK Research and Innovation, 2018) which is investigating purines as a potential biomarker of stroke in the pre-hospital setting.

Other stroke diagnostic devices are currently being investigated including electromagnetic measurement performed by the Cerebrotech visor (Cerebrotech Medical Systems, 2018), the evoked potential prototype developed by Alpha Stroke (Forest Devices, 2018) and the microwave based Strokefinder device (Medfield Diagnostics, 2018). Ultrasound is also being investigated for its potential to improve pre-hospital stroke diagnosis (Holscher *et al.*, 2008) and treatment (Hitchcock and Holland, 2010). All of these devices may lead to improvements in stroke diagnoses, but how they interact with existing stroke identification tools, the cost-effectiveness and their impact on patient outcomes will need to be considered and evaluated.

4.0.8 Future research

Pre-hospital research has come a long way since Callaham described the "*scanty science of prehospital emergency care*" (Callaham, 1997). Paramedic involvement in pre-hospital

research is a growing area (NIHR Dissemination Centre, 2016), and research is an emerging career choice for paramedics (McClelland, 2013). There are a number of areas which could have been explored, but were beyond the scope and resources of this thesis.

The linkage of pre-hospital data with final patient diagnoses underpinned this work and provided original data on the accuracy of paramedic stroke identification. Expansion and continuation of this data linkage could be used to refine and improve pre-hospital stroke identification and provide feedback to ambulance and stroke services about rates and types of SM patients. This type of data could be added to national audits like SSNAP or the ambulance quality indicators which currently do not include a measure of pre-hospital diagnostic accuracy. In the context of the service and technology developments described above, this would enable observation of the care delivery impact following the introduction of interventions such as: SM identification assessment; pre-hospital training; enhanced imaging; or novel diagnostics. Looking further ahead, linked pre-hospital and hospital data could be analysed using machine learning, which is already being considered in some areas of stroke care (Kamal *et al.*, 2018), in order to develop, and improve upon, tools for purposes such as SM identification.

One of the exclusion criteria in STEAMv2 development was a reduced level of consciousness represented by a GCS<8. This was a small population of patients (n=362 (6%) across the four hospital trusts) who would traditionally be pre-alerted to the nearest ED based on their reduced GCS. How patients with a significantly reduced level of consciousness due to a stroke could be more accurately identified would be an interesting question to explore, because if the underlying condition is a stroke the nearest ED may not be the most suitable location for their ongoing care.

If STEAMv2 were to be developed further, access to new data for further refinement and validation would be necessary and additional data, such as time since onset or variables related to functional diagnoses, could be sought. STEAMv2 could also be tested in combination with a biomarker or novel diagnostic tech to explore their combined performance. STEAMv2 could also be compared with other SM tools if all the necessary variables were available. If a pre-hospital thrombectomy screening tool was introduced then this type of project could be repeated but focussed on SM identified by the new screening tool.

4.0.9 Conclusions

Pre-hospital stroke care focusses on the identification of suspected stroke patients and rapid transport to specialist care due to the time dependent nature of acute stroke treatment. The FAST remains the standard tool used by UK pre-hospital services to identify stroke patients. All pre-hospital stroke identification tools seek to identify the maximum number of stroke patients using basic observations and symptoms, i.e. they prioritise sensitivity over specificity. Due to the non-specific nature of stroke symptoms, and the many other conditions producing similar symptoms, a significant percentage of suspected stroke patients have a final SM diagnosis. Although difficult to quantify, it is likely that this has a negative effect on outcomes and resources through unnecessary thrombolysis and "bed blocking" on HASU.

A small number of SM presentations can be accurately identified in the pre-hospital setting based on currently available data using the STEAMv2 tool. STEAMv2 was robustly developed based on pre-hospital data with paramedic and hospital clinician input throughout the process. Whilst both groups were supportive of the idea of identifying SM patients, the risks of a very small proportion of stroke patients missing, or having delayed, treatment were perceived to outweigh the potential benefits in their current systems.

SM will remain an inevitable part of the current system of acute stroke care, especially in the absence of objective diagnostic tests. Increased centralisation of stroke services and the need to accurately identify patients suitable for thrombectomy means that incremental improvements in pre-hospital stroke identification are desirable. Although STEAMv2 may not have sufficient impact by itself for wide-spread implementation, it is simple and would not require new resources. A tool like STEAMv2, possibly with the inclusion of more physiological parameters or in combination with novel diagnostic technology, may provide an acceptable and affordable approach to identification of SM. SM identification would allow better use of finite specialist resources in a system where patients faced longer transfers and there were fewer stroke units. In the current system, the lack of quantifiable benefits and the perceived risks due to delayed identification of some stroke patients mean that STEAMv2 is probably not applicable in practice.

Appendices

Appendix A. Literature search strategy from systematic review of stroke mimics

Database: Embase

1 differential diagnosis/
2 diagnostic error/
3 false positive result/
4 mimic.mp.
5 1 or 2 or 3 or 4
6 exp cerebrovascular accident/di [Diagnosis]
7 exp transient ischemic attack/di [Diagnosis]
8 stroke.mp.
9 6 or 7 or 8
10 5 and 9

Database: Ovid MEDLINE(R)

1 exp Stroke/di [Diagnosis]
2 cerebrovascular accident.mp.
3 exp Ischemic Attack, Transient/di [Diagnosis]
4 1 or 2 or 3
5 mimic.mp.
6 diagnosis, differential/ or false positive reactions/
7 5 or 6
8 4 and 7

Database: CINAHL

S1 (MH "Stroke+/DI") OR cerebrovascular accident OR transient ischemic attack
S2 (MH "Cerebral Ischemia, Transient/DI")
S3 "mimic"
S4 (MH "Diagnosis, Differential")
S5 (MH "False Positive Results")
S6 S3 OR S4 OR S5
S7 (S3 OR S4 OR S5) AND (S1)

Appendix B. QATSDD Scoring

QATSDD Criteria																
Paper	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**Total**	**%**
Aiyesimoju et al	0	2	3	0	3	1	1	3	0	3	1	1	0	0	18	43%
Ali et al	0	2	3	0	3	3	0	3	0	3	3	0	0	3	23	55%
Alves et al	0	3	3	0	2	0	0	2	0	3	2	0	0	0	15	36%
An et al	0	1	3	0	1	3	2	3	3	3	3	3	0	2	27	64%
Artto et al	0	3	3	0	3	3	3	3	0	3	3	2	0	3	29	69%
Asaithambi et al	0	3	3	0	2	1	0	2	0	3	3	1	0	1	19	45%
Ay et al	0	2	3	0	3	3	0	3	0	3	3	0	0	0	20	48%
Barker et al	0	3	3	0	3	3	0	3	0	3	3	0	0	2	23	55%
Brandler et al	0	3	3	3	3	2	2	3	0	3	3	3	0	3	31	74%
Bray et al	0	3	3	0	2	3	3	2	3	3	3	3	0	1	29	69%
Brunser et al	0	3	3	0	3	3	0	3	0	3	3	0	0	3	24	57%
Chang et al	0	3	2	0	3	1	1	3	0	3	3	0	0	2	21	50%
Chen et al	0	3	3	0	2	1	1	3	0	3	3	0	0	2	21	50%
Chernyshev et al	0	2	3	0	3	1	1	3	0	3	3	0	0	3	22	52%
Clarey et al	0	3	3	3	3	3	3	3	3	3	3	0	0	2	32	76%
Dassan et al	0	2	1	0	1	3	2	2	1	3	3	2	0	2	22	52%
Dawson et al	0	3	3	0	3	2	2	2	0	3	3	3	0	2	26	62%
Eichel et al	0	3	3	0	2	3	3	3	0	3	2	3	0	3	28	67%
El Husseini & Goldstein	0	2	2	0	3	1	0	3	0	3	3	0	0	2	19	45%
Ferro et al	0	3	3	0	2	3	2	3	0	1	3	0	0	1	21	50%
Foerch et al	0	3	2	0	2	3	3	2	0	3	3	0	0	3	24	57%
Forster et al	0	3	2	0	3	3	3	3	0	3	3	3	0	3	29	69%
Gargalas et al	0	3	3	0	2	3	3	3	3	3	3	3	0	3	32	76%
Gioia et al	0	3	3	0	3	3	1	3	0	0	3	3	0	3	25	60%
Gonzalez-Garcia et al	0	3	3	0	2	3	1	2	0	1	1	0	0	2	18	43%
Goyal et al	0	3	3	2	3	1	3	2	0	3	3	3	0	2	28	67%

QATSDD Criteria cont.																
Paper	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**Total**	**%**
Goyal et al	0	3	3	0	3	3	3	3	0	3	3	3	0	2	29	69%
Guillan et al	0	1	3	0	3	3	2	3	0	3	3	0	0	2	23	55%
Hand et al	0	3	2	3	3	3	2	3	3	3	3	3	0	2	33	79%
Hatzitolios et al	0	1	3	0	2	3	1	2	0	2	2	0	0	0	16	38%
Hemmen et al	0	3	3	0	3	3	3	2	0	3	3	0	0	2	25	60%
Jiang et al	0	3	3	0	3	3	3	3	3	3	3	3	0	3	33	79%
Karlinski et al	0	3	3	0	3	3	0	3	0	3	3	2	0	1	24	57%
Knauer et al	0	3	2	0	1	3	3	3	3	3	3	3	0	2	29	69%
Kose et al	0	3	3	0	2	3	0	2	0	3	3	0	0	3	22	52%
Kothari et al	0	3	3	0	3	3	1	3	0	3	3	1	0	3	26	62%
Laskowitz et al	0	3	3	0	3	3	3	3	3	3	3	3	0	3	33	79%
Lewandowski et al	0	3	2	0	3	3	0	3	0	3	3	0	0	2	22	52%
Liberman et al	0	3	2	0	2	3	3	3	0	3	3	0	0	1	23	55%
Libman et al	0	2	2	0	1	3	0	1	0	3	3	2	0	0	17	40%
Luger et al	0	3	3	0	2	3	3	1	3	3	3	3	0	3	30	71%
Mao et al	0	3	3	0	1	1	1	1	0	3	3	2	0	2	20	48%
Martin et al	0	3	3	0	3	3	3	3	0	3	3	2	0	1	27	64%
Mehta et al	0	2	3	0	2	1	1	3	0	3	3	2	0	2	22	52%
Merino et al	0	3	3	0	3	3	1	3	0	3	3	3	0	3	28	67%
Montaner et al	0	3	2	0	3	3	3	3	3	3	3	3	0	3	32	76%
Natteru et al	0	3	3	0	3	1	1	1	2	3	3	1	0	2	23	55%
Nor et al	0	3	3	0	3	3	3	3	0	3	3	3	0	2	29	69%
Norris & Hachinski	0	2	3	0	3	0	1	3	0	1	1	0	0	0	14	33%
O'Brien et al	0	3	3	0	2	3	3	3	0	3	3	0	0	1	24	57%
O'Connell et al	0	3	2	0	1	3	3	1	3	3	3	3	0	2	27	64%
Quenardelle et al	0	3	3	0	3	3	3	3	0	3	3	3	0	2	29	69%

QATSDD Criteria cont.																
Paper	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**Total**	**%**
Reid et al	0	3	3	0	3	3	1	3	0	2	2	0	0	0	20	48%
Rostanski et al	0	3	3	0	3	2	0	2	0	3	3	2	0	2	23	55%
Sarikaya et al	0	3	3	0	2	3	1	3	0	3	3	1	0	3	25	60%
Scott & Silbergleit	0	3	3	0	2	3	3	2	0	3	3	1	0	3	26	62%
Sequeira et al	0	3	3	0	3	2	1	3	0	3	3	1	0	2	24	57%
Sharma et al	0	3	3	0	2	3	3	3	3	3	3	3	0	3	32	76%
Sivakumaran et al	0	3	3	0	3	1	0	2	0	3	3	1	0	2	21	50%
Taguchi et al	0	3	2	0	2	1	0	2	0	3	3	1	0	2	19	45%
Tobin et al	0	3	3	0	3	3	3	1	0	3	3	3	0	0	25	60%
Tsivgoulis et al	0	3	3	2	3	3	3	3	3	3	3	3	0	3	35	83%
Tsivgoulis et al	0	3	3	0	3	3	1	3	0	3	3	3	0	2	27	64%
Tuntiyatorn et al	0	3	3	0	3	3	1	3	0	3	3	2	0	2	26	62%
Wendt et al	0	3	3	0	3	3	3	3	0	3	3	3	0	2	29	69%
Whiteley et al	0	3	3	0	2	3	3	3	3	3	3	3	0	2	31	74%
Winkler et al	0	3	3	0	2	3	3	3	0	3	3	0	0	2	25	60%
Wolf et al	0	3	2	0	3	0	0	2	0	3	3	1	0	2	19	45%
Zinkstok et al	0	3	3	0	3	3	3	3	0	3	3	0	0	2	26	62%

QATSDD

Criteria	
A	**Explicit theoretical framework**
B	**Statement of aims/objectives in main body**
C	**Clear description of research setting**
D	**Evidence of sample size consideration in terms of analysis**
E	**Representative sample of target group of a reasonable size**
F	**Description of procedure for data collection**
G	**Rationale for choice of data collection tools**
H	**Detailed recruitment data**
I	**Statistical assessment of reliability and validity of measurement tools**
J	**Fit between stated research question and method of data collection**
K	**Fit between research question and method of analysis**
L	**Good justification for analytical method selected**
M	**Evidence of user involvement in design**
N	**Strengths and limitations critically discussed**

Appendix C. Survey questions

1. Do you agree to continue with the survey? *Yes, No*
2. What is your age? *<18, 18-20, 21-29, 30-39, 40-49, 50-59, 60+*
3. Are you male of female? *Male, Female*
4. How long have you worked in pre-hospital care? *0-2 years, 3-5 years, 6-10 years, 11-20 years, more than 20 years*
5. What is your current job role? *Paramedic, Specialist paramedic, Advanced Paramedic, Consultant Paramedic, Other paramedic, Non-paramedic*
6. Is your main job working for an NHS ambulance trust? *Yes, No*
7. Which service do you work for? *East of England Ambulance Service NHS Trust, East Midlands Ambulance Service NHS Trust, Isle of Wight Ambulance Service, London Ambulance Service NHS Trust, National Ambulance Service (Ireland), North East Ambulance Service NHS Foundation Trust, North West Ambulance Service NHS Trust, Northern Ireland Ambulance Service Health and Social Care Trust, South West Ambulance Service NHS Foundation Trust, South Central Ambulance Service NHS Foundation Trust, South East Coast Ambulance Service NHS Foundation Trust, Scottish Ambulance Service, Welsh Ambulance Services NHS Trust, West Midlands Ambulance Service NHS Foundation Trust, Yorkshire Ambulance Service NHS Trust*
8. Where do you mainly work? *HEMS, Hospital, Military, Primary care, Private ambulance service, Remote/offshore, SAR, University, Other (please specify)*
9. In which area do you mainly work? *East of England, East Midlands, Isle of Wight, London, North East, North West, Northern Ireland, South West, South Central, South East Coast, Scotland, Wales, West Midlands, Yorkshire, Other (please specify)*
10. What is your highest level of education relevant to your paramedic role? *IHCD Paramedic, FdSc, BSc, PGCert, PGDip, Masters, Doctorate*
11. How did you qualify as a paramedic? *IHCD, University, Other (please specify)*
12. Did your initial training about stroke consider it as a condition in isolation or was stroke covered as part of a wider neurological topic? *Stroke covered in isolation, Stroke covered as part of wider neurology*

13. Based on your current knowledge of stroke care how would you classify your initial training? *Inadequate, Adequate, Excessive, Any comments on your initial stroke training?*
14. Would you like more training on prehospital stroke care? *Yes, No, Unsure*
15. Do you think paramedics as a group need more training on prehospital stroke care? *Yes, No, Unsure*
16. What type of training would you like regarding stroke going forward?
17. Have you completed any Continuing Professional Development (CPD) activities focussed on stroke since qualifying as a paramedic? *Yes, No*
18. What type of stroke CPD have you completed? *Ambulance service based training University based training, Conference with stroke related content, Stroke specific lecture, seminar or workshop, Self directed learning (offline), Self directed learning (online), Other (please specify)*
19. How many hours CPD relevant to stroke have you done in the past 12 months? (approximately)
20. What stroke assessment tools do you use to assess suspected stroke patients in your prehospital practice? *Cincinnati Prehospital Stroke Scale (CPSS), Face Arms Speech Time (FAST),*

    Los Angeles Prehospital Stroke Screen (LAPSS), Melbourne Ambulance Stroke Screen (MASS), Miami Emergency Neurologic Deficit (MEND), National Institutes of Health Stroke Scale (NIHSS), Recognition of Stroke in the Emergency Room (ROSIER), Los Angeles Motor Scale (LAMS), Rapid Arterial oCclusion Evaluation (RACE), Other (please specify)
21. What stroke assessment tools have you been trained to use? *CPSS, FAST, LAPSS, MASS, MEND, NIHSS, ROSIER, LAMS, RACE, Other (please specify)*
22. How would you rate your confidence when dealing with the following time critical conditions: Sepsis, STEMI, Stroke, Major trauma? *Very little confidence, Little confidence, Neutral, Confident, Very confident*
23. To what extent do you think that prehospital actions influence a patient's outcome in the following time critical conditions: Sepsis, STEMI, Stroke, Major trauma? *Very little*

influence, Little influence, Neutral, Some influence, Very high influence

24. How do you think prehospital care has changed over the course of your career for the following time critical conditions: Sepsis, STEMI, Stroke, Major trauma? *Much worse, Slightly worse, No change, Slightly better, Much better*
25. Where do you take most stroke patients in your region? *Direct to scan, Emergency Department (ED), Hyper Acute Stroke Unit (HASU), Stroke ward, Other (please specify)*
26. Does where you take stroke patients change depending on the time of day or day of the week? *No, Yes - by time of day, Yes - by day of the week, Yes - by time and day*
27. Do you have access to any form of telemedicine for stroke patients? *Yes, No, If yes, please describe what form this takes*
28. Do you get any feedback on stroke patients you treat and transport? *Yes (formal),Yes (informal), No*
29. Do you think that feedback on stroke patients you treat would be useful to you as a paramedic? *Yes, No, If yes how would you like the feedback and to what level of detail?*
30. Would you routinely perform an ECG on a stroke patient? *Yes - all stroke patients, Yes - only if they had chest pain, Not routinely, Any comments on ECGs on stroke patients*
31. Are you currently involved in any prehospital stroke research (apart from this survey)? *Yes, No*
32. What prehospital stroke research are you involved in? *PASTA, RIGHT2, TIER, Other (please specify)*
33. Had you heard of the term 'stroke mimic' before today? *Yes, No*
34. What do you understand by the term 'stroke mimic'? *Where a patient appears to be suffering from a different condition but their symptoms are due to a stroke., Where a patient appears to be having a stroke but their symptoms are due to a different condition., Where a patient describes stroke-like symptoms but is symptom free when you arrive.*
35. What proportion of suspected strokes admitted by ambulance do you think are stroke mimics?

36. What do you think are the three most common stroke mimics seen in prehospital care? *Brain tumours, Headache, Mental illness, Metabolic disorders, Migraine, Sepsis, Seizures, Syncope, Toxins (including alcohol), Vertigo*
37. Do you think a tool that calculates the chance of a suspected stroke patient having a stroke mimic condition would be useful in prehospital care? *Yes, No, Unsure*
38. In what format would a stroke mimic tool be most useful for the prehospital setting? *Paper based, Electronic (stand alone app or program), Electronic (built into electronic patient record device), Other (please specify)*
39. How acceptable would it be for paramedics to treat a suspected stroke (FAS+ve) patient differently (i.e. take to ED instead of HASU) based on a test that indicates a high probability that the patient is a stroke mimic? *Totally unacceptable, Mostly unacceptable, Neutral, Mostly acceptable, Totally acceptable*
40. How certain that a patient was a stroke mimic would you need to be to decide not to follow your normal stroke care protocol?
41. Any thoughts or comments about prehospital identification and treatment of stroke mimics?
42. Do you have access to referral pathways for TIAs in your region? *Yes, No, Unsure*
43. Do you have access to TIA clinics in your region? *Yes, No, Unsure*
44. Do you treat TIA with antiplatelets in your practice? *Yes (aspirin), Yes (other antiplatelet), No*
45. Do you use a risk stratification tool for TIA patients? *Yes, No*
46. Which risk stratification tool do you use on TIA patients? *ABCD2, Other (please specify)*
47. What is the current timeframe for thrombolysis in stroke patients? *Up to 2.5 hours, Up to 3.5 hours, Up to 4.5 hours, Up to 5.5 hours*
48. Have you heard of intra arterial thrombectomy for stroke? *Yes, No*
49. What percentage of your workload do you think stroke makes up?
50. If you have any comments you want to make on the current state of prehospital stroke care please record them below.

Appendix D. Example EPRF

North East Ambulance Service NHS

NHS Trust

NHS CONFIDENTIAL: PERSONAL DATA ABOUT A PATIENT Created on: 06/05/2015 13:55:33	FINALISED: YES	Incident Number: 123456789 Patient 1of 1 EPRF Number: 2776247

PATIENT DETAILS

PracticePractice,PracticePractice

65 Years (Actual)	Sex: Not Known	D.o.B 01/01/1950	NHS No.:
Chief Complaint: Stroke / TIA;		Clinical Impression: Neurological: Stroke;	

COMMENTS

This is a practice PCR.

VITAL SIGNS

Time	HR	RR	BP-Sys	BP-Dia	SPO2	Peak Flow	EtCO2	BM	TEMP	Pain: Numeric	Pain: Visual	GCS	Position	Done By
M-11:10:57	90 BPM	12 BPM	165 mmHg	95 mmHg	98 % - RA;			'5.2' mmol/L	37 Celsius	0		E 4 V 4 M 6 14	Sitting	GM

INJURY

ABCD - PHYSICAL EXAM

		ACTUAL	PERTINENT NEGATIVES
Gen	Primary Survey Summary:	Normal	
	Patient Position Found:	Seated	
	Alcohol/ Drug Use Indicators:	Patient denies alcohol use; Patient denies drug use;	
	AVPU:	Alert;	
	FAS Test:	Positive;	
A	Airway Status:	Status: Clear; ;	
B	Breathing Sounds:	Breathing Sounds: Normal/Clear;	
	Breathing Signs:	No abnormal breathing signs;	
	Breathing Quality:		
	Respiratory Rate:	Regularity: Normal;	
C	Pulse:	Site: Right Radial; Rate (per/min): Normal; Rhythm: Regular; Strength: Strong;	
D	Pupils:	(L): Size: 3mm; (L): Reactivity: Brisk; (L): Quality: Normal; (R): Size: 3mm; (R): Reactivity: Brisk; (R): Quality: Normal;	

EXAMINATION

	ACTUAL	PERTINENT NEGATIVES

EXAMINATION - EXTENDED SYSTEMS

	ACTUAL	PERTINENT NEGATIVES

EXAMINATION - PHYSICAL EXAM

	ACTUAL	PERTINENT NEGATIVES

PAST MEDICAL HISTORY

	ACTUAL	PERTINENT NEGATIVES

OUTCOMES

MISCELLANEOUS INFORMATION

Condition of Patient at Destination: Improved;

Discharge Considerations	ACTUAL	PERTINENT NEGATIVES
	ACCOMMODATION: House; **ACTIVITIES OF DAILY LIVING:** Normally self caring;	

DEMOGRAPHICS

PATIENT DETAILS	NEXT OF KIN	GP DETAILS
First Name: PracticePractice **Last Name:** PracticePractice **Date of Birth:** 01/01/1950 **Address1:** **Address2:** **City:** **County:** **Country:** **Post Code:** **Home:** **Mobile:** **NHS No.:** **Religious Affiliation:** Patient Religion Unknown	**First Name:** **Last Name:** **Date of Birth:** **Address1:** **Address2:** **City:** **County:** **Country:** **Post Code:** **Home:** **Mobile:** **Relationship:**	**Surgery Name:** - 728 COVENTRY ROAD SURGERY **Address1:** 726 - 728 COVENTRY ROAD **Address2:** SMALL HEATH **City:** BIRMINGHAM **County:** **Country:** **Post Code:** B10 0TU

INCIDENT

	Time	Details	Delays/Divert
Incident Date / Time:	06/05/2015 13:56:02	**Location Type:** Home; **Address 1:** 123 Somewhere Street **Address 2:** Anywhere **Post Code:** NE1 2AB	
Transport Request Call Connect Time:			
Dispatched:	06/05/2015 10:57:24	**Call Type:** Emergency **Location Type:** Home; **Address 1:** 123 Somewhere Street **Address 2:** Anywhere **Post Code:** NE1 2AB	
Mobile:	06/05/2015 10:58:25	**Incident Number:** 123456789 **Number of Patients:** 1	
Arrive Scene:	06/05/2015 11:05:26		
At Patient Side:			
On Scene Transfer:			
Depart Scene:	06/05/2015 11:55:29		**Response Outcome:** Treated and Transported;
Arrive Destination:	06/05/2015 12:10:30	**Destination Type:** Emergency Department;	

		Receiving Location: RVI	
Care Transfer:	06/05/2015 12:15:06		
Available:			
RL Pre-Alert:			
RL ETA:			

VEHICLE(S)

Trust Name	Agency Number	District / Region	Call Sign	Vehicle Call Sign	Vehicle ID	Primary Role of Unit	Vehicle Type	Service Level	Vehicle Base Station
			999				Emergency Ambulance		Headquarters

CREW MEMBERS

Name	Role	Level	Position	ID Number	Registration	Type	Current Crew
Shaggy Shaggy			Secondary Crew		PA98765	Paramedic	Yes
Doo Scooby			Unspecified Crew			Technician	Yes
Doo Scrappy			Third Crew		PA12345	Paramedic	Yes
McClelland Graham	User	Paramedic	Primary Crew		PA24327		Yes

STROKE SCALE

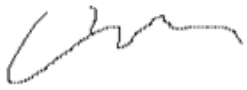
Time	Facial Droop	Arm Drift	Speech	Test Result
14:05:17	Normal	Normal	Abnormal	Positive

SIGNATURE

Primary Crew

Name of signer: McClelland Graham

Date/Time of signature: 06/05/2015 14:07:28



PDS LOOKUP

NHS Number :	**Status** : PDS trace was invoked and a response was received. A match was not found.

MESSAGE STATUS SUMMARY

NHS Number :	
	06/05/2015 14:04:49 : Sending GP email : Not performed [31]
	06/05/2015 14:04:49 : Sending pre-admit message : Not performed [41]

Created on: 06/05/2015 13:55:33 Incident Number: 123456789

Appendix E. Free-text data collection protocol

Title: PaStraMi Free-text data extraction

Objective

Extraction of relevant stroke data from the free-text section of the North East Ambulance Service (NEAS) electronic patient record form (EPRF).

Dataset

NEAS stroke data from PaStraMi service evaluation project.

Method

Data are to be indicated as present with a '1' and left blank if not present.

Data are to be considered present if the EPRF indicates that the NEAS crew attending the patient directly report the sign or symptom at the time of their attendance. Signs and symptoms that resolved prior to NEAS attendance are not to be included.

Data extraction check

A sample of PaStraMi cases with data recorded in the comments section in the form of narrative text will be checked by a second researcher to report on extraction of relevant data. A sample of 60 cases will be checked. The sample will be randomly identified from cases with any freetext data.

A level of interpretation is necessary for this type of narrative text so the cross checking will be done by a clinician with a similar background and level of training to the original data extractor.

Guidance

FAST+ve Documented means where some form of positive FAS test is indicated, not the signs, symptoms or observations that comprise the test.

Eye Issues means signs recorded by the crew of gaze deviation, fixed stare or the like.

Vision issues means patient reported symptoms of some form of visual disturbance.

Output

This process will allow level of agreement to be described using Cohen's kappa as a measure of inter-rater agreement in terms of number of freetext data points and agreement in the specific data points extracted.

Appendix F. NEAS and NHCT data linking protocol

Title: PaStraMi Dataset Development Protocol (NEAS and Northumbria)

Glossary

CAD – Computer Aided Dispatch, unique identifying number for ambulance cases
EPRF – Electronic Patient Report Form, documentation of patient contact with ambulance service
HES – Hospital Episode Statistics, details of admitted NHS patients
NEAS – North East Ambulance Service NHS Foundation Trust
Northumbria – Northumbria Healthcare NHS Foundation Trust
SSNAP – Sentinel Stroke National Audit Programme, national database of stroke patients
TIA – Transient Ischaemic Attack, stroke like symptoms lasting less than 24 hours

Objective

Confirmation of hospital diagnosis of stroke, TIA and stroke mimic amongst a cohort of NEAS admissions who were given a paramedic diagnosis of suspected stroke.

Initial main dataset: NEAS

Data will be initially sourced from NEAS through a request placed with NEAS informatics.

Timeframe: all cases between 01/06/2013 00:00 and 31/05/2016 23:59

Identified by clinical impression includes stroke.

The data fields requested include: Case Identifiers, Name, Age, Date & Times, Chief Complaint, Impression, Primary Survey Information, Vitals and History, Receiving Hospital and freetext comments

Matching outcome dataset: Northumbria

The NEAS suspected stroke cohort will be cross-referenced with:

1. Northumbria SSNAP data for the same time interval
2. HES if not found in SSNAP

Matching

Data will be matched using a 5 stage process:

Step 1. Where Northumbria SSNAP data reports a CAD number that matches with a NEAS case of suspected stroke this will be classified as a <u>true stroke</u>.

Step 2. Where no CAD number is reported, cases will be matched in SSNAP on a combination of hospital, age, gender and time of arrival at the hospital. Due to variation in when and how ambulance arrival time is reported time +/- 20 minutes will be accepted. If time plus all other criteria match then this will be classified as a true stroke. If cases match on hospital + 2/3 factors then continue to step 3.

Step 3. If unable to make a definite match based on the criteria in step 2 then further attempts to match can be made using patient postcode, onset time (if documented), date of birth plus any other data in the free text that is available. Individual NEAS EPRFs may need to be accessed to check data or gather additional data. Positive match as a true stroke requires consistent matching across the majority of criteria or clear explanation of differences.

Step 4. If no match for NEAS suspected stroke (i.e. potential stroke mimic or TIA) then case details to be passed to Northumbria Healthcare NHS Foundation Trust including name; gender; age; hospital; date and time of admission; CAD number to identify final diagnosis (primary code) using HES.

Step 5. If final diagnosis is available from Northumbria remaining NEAS cases to be classified as true stroke, stroke mimic or TIA. If unable to match on available data record case as unmatched.

Data matching check

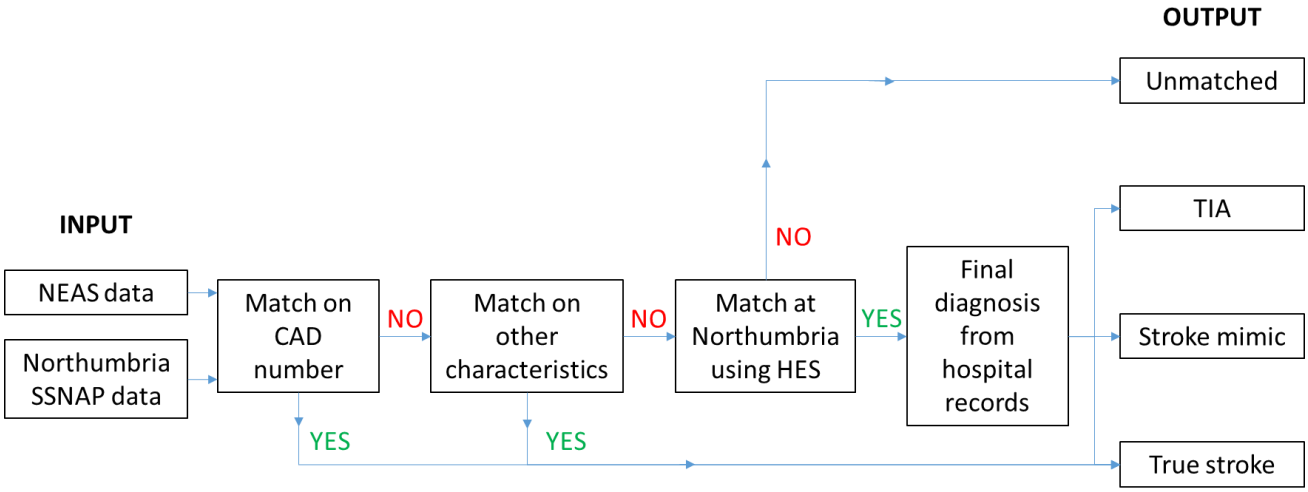
A 10% sample of 30 cases (based on 1,800 total cases, 50% (n=900) match in total, 2/3rd (600) match at steps 1 and 2 leaving 300 match at step 3) matched at step 3 will be passed to a second researcher to check for agreement on the matching process. Level of agreement will be reported on using Cohen's kappa as a measure of inter-rater agreement.

Missing and unmatched data

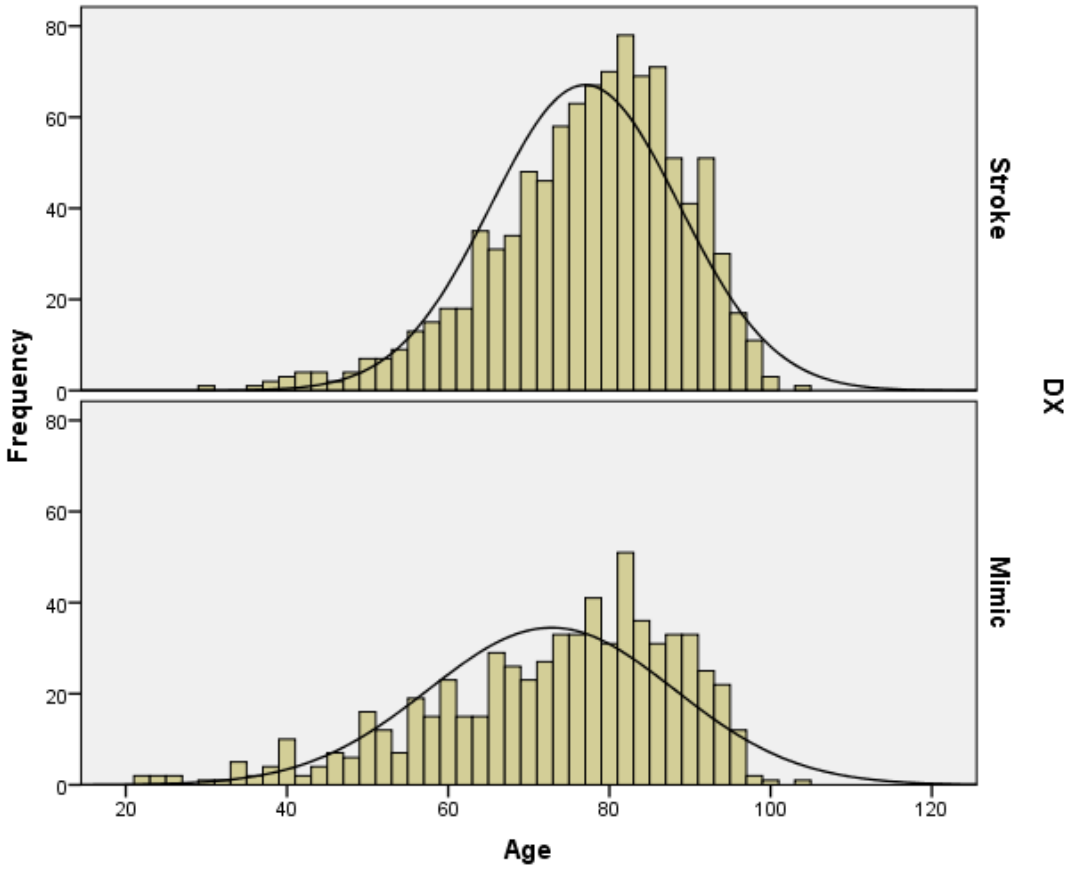
If data is missing from the dataset supplied by NEAS informatics then access to the source material (in the form of the EPRF) can allow data fields to be completed or indicated as missing data.

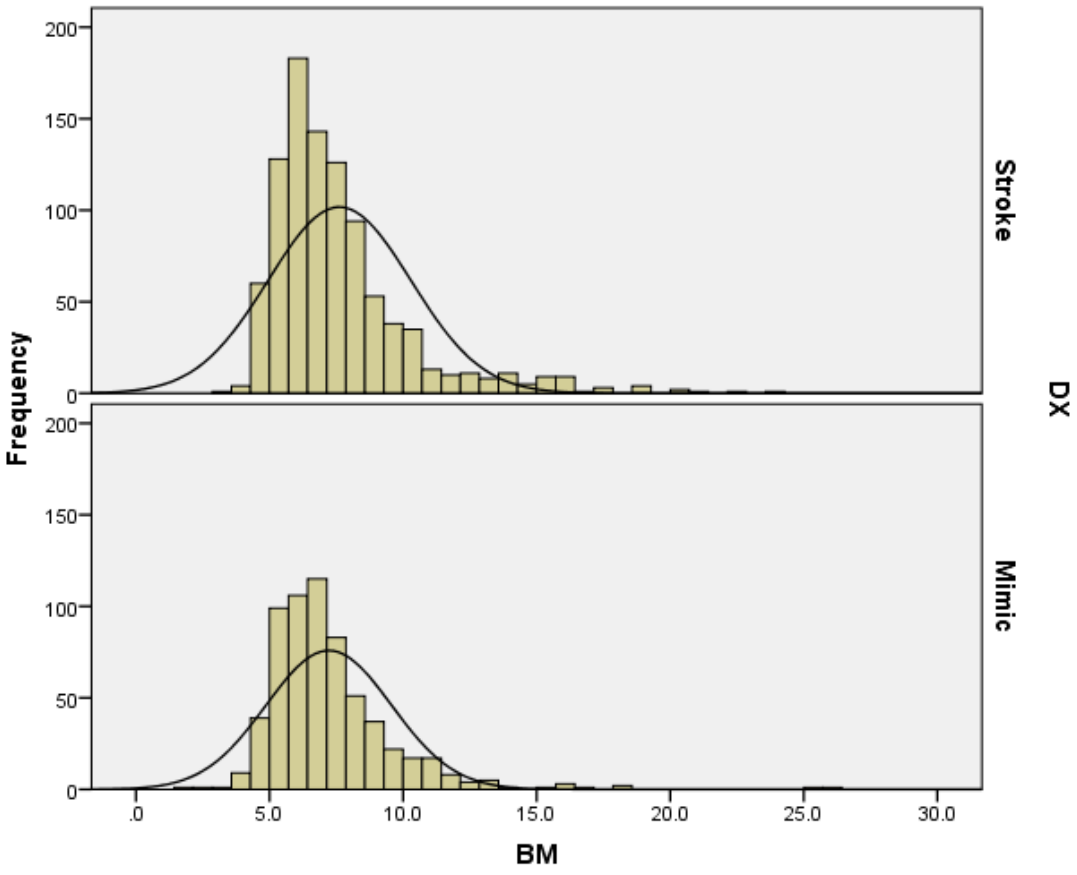
Cases in the NEAS cohort which cannot be identified in SSNAP or HES will be reported by number and clinical characteristics. A sample of unmatched cases will be compared with the matched cases to identify the presence of any systematic bias.

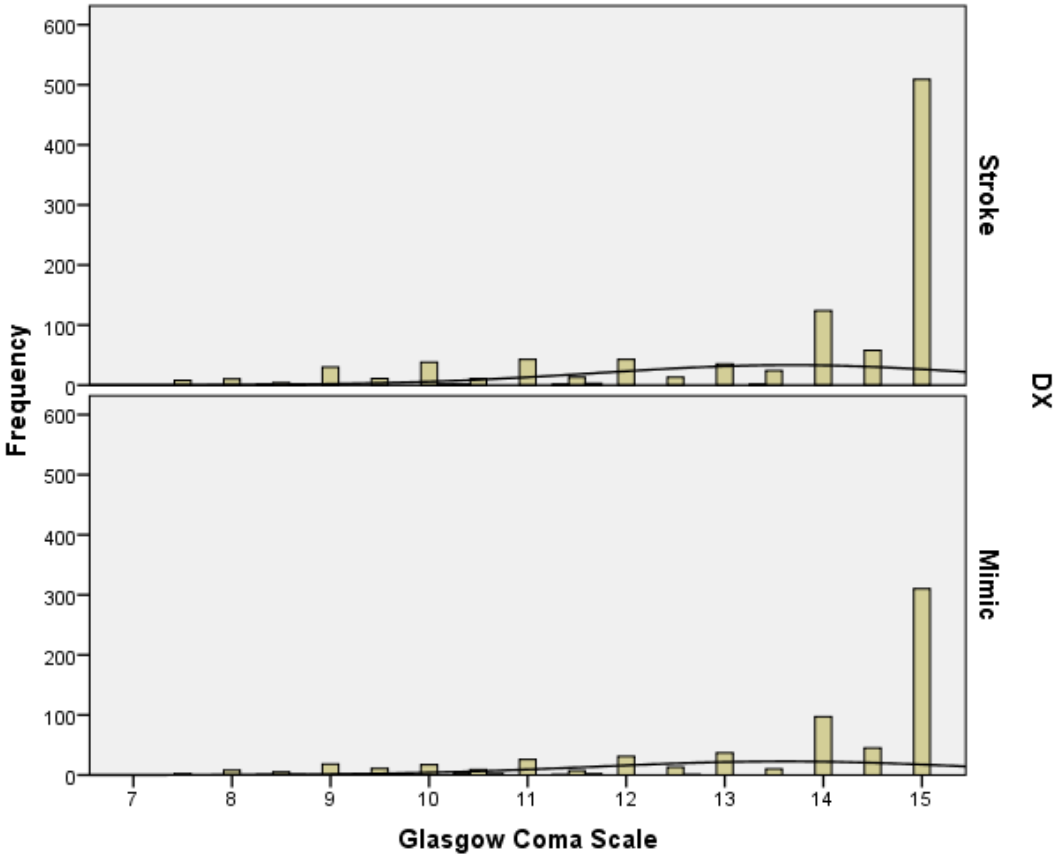
Data flow diagram

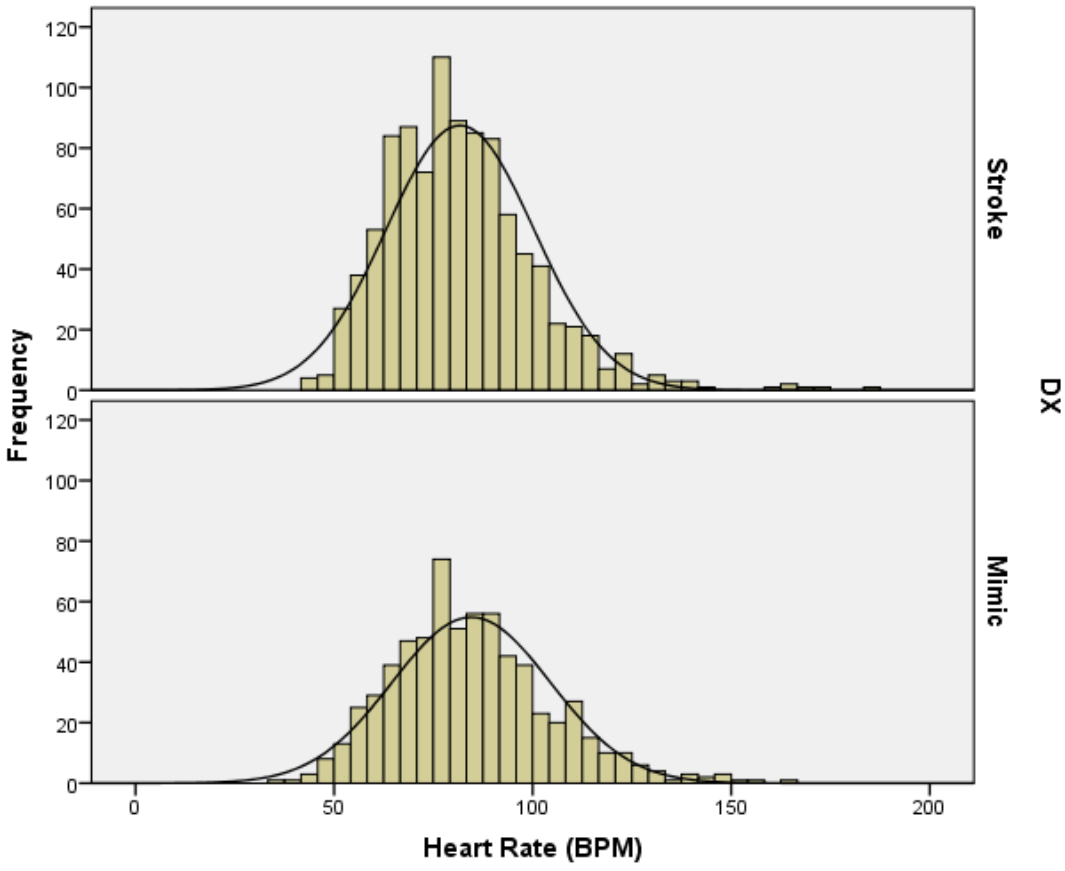


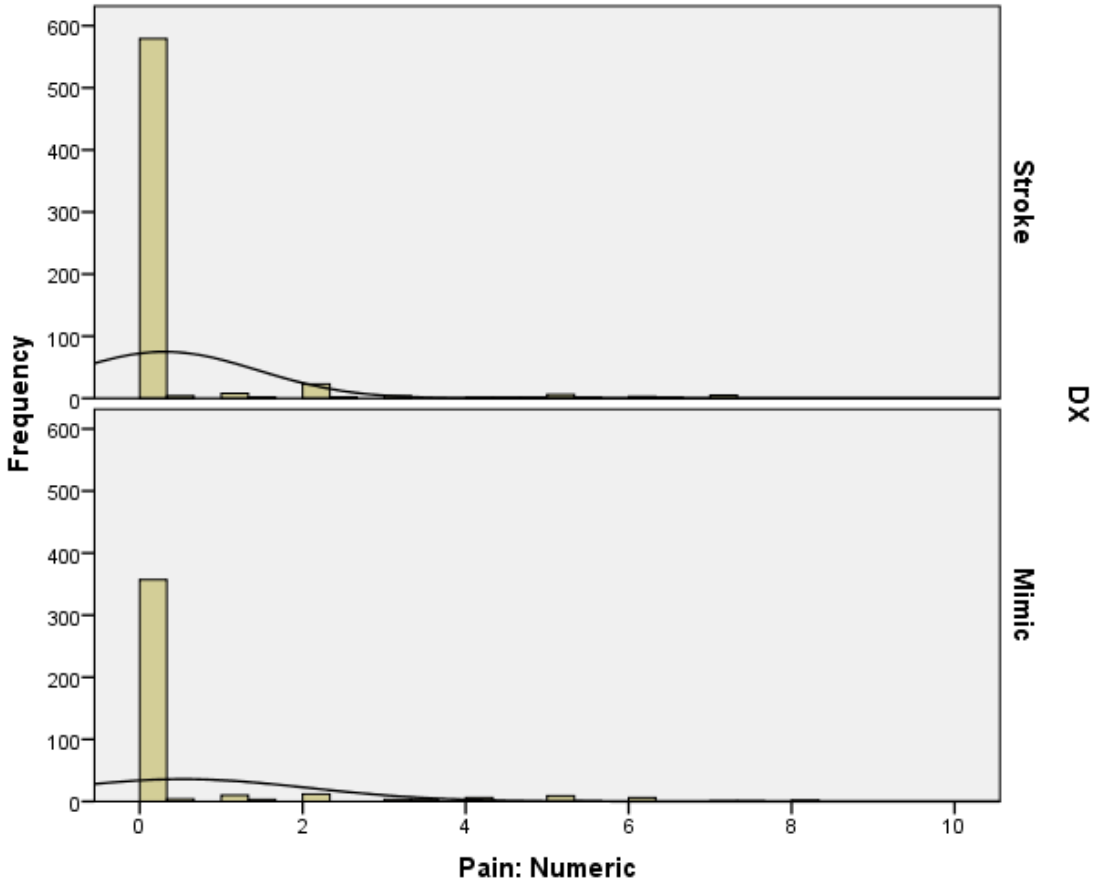
Appendix G. Frequency distribution plots

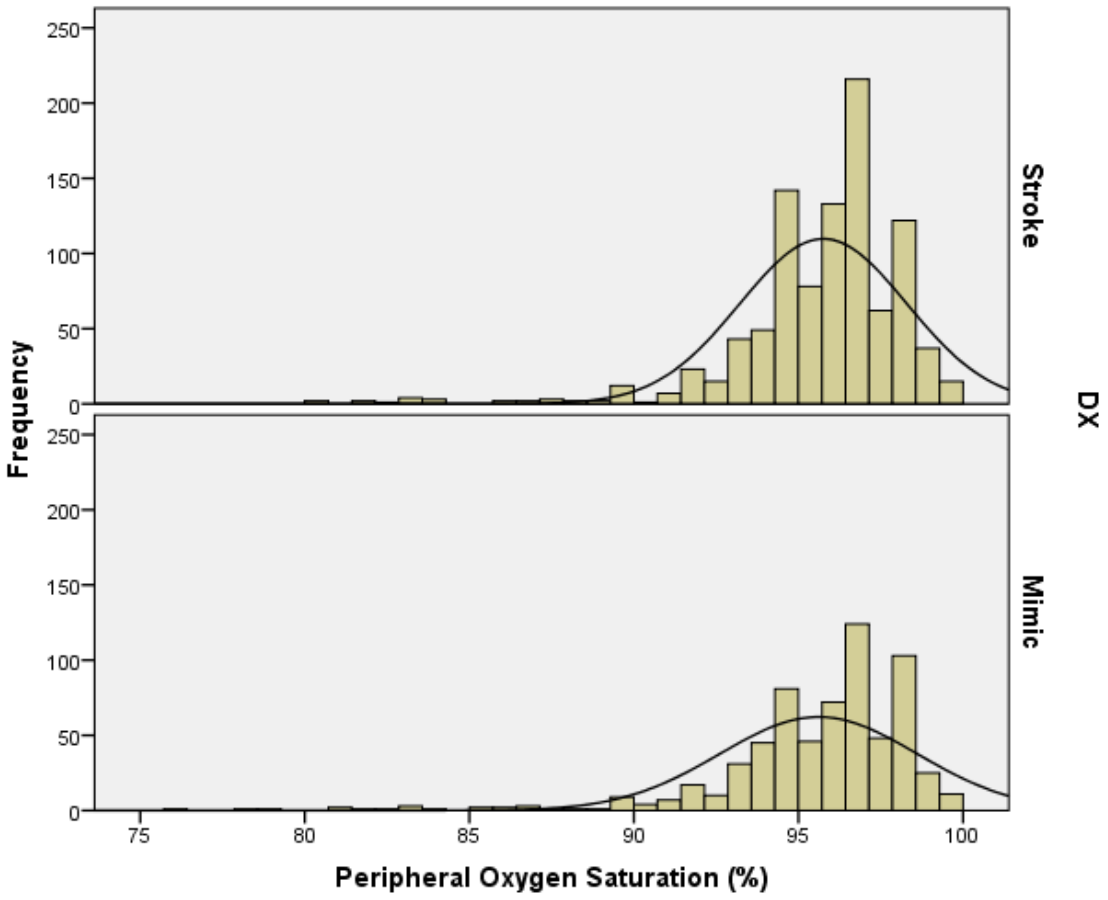


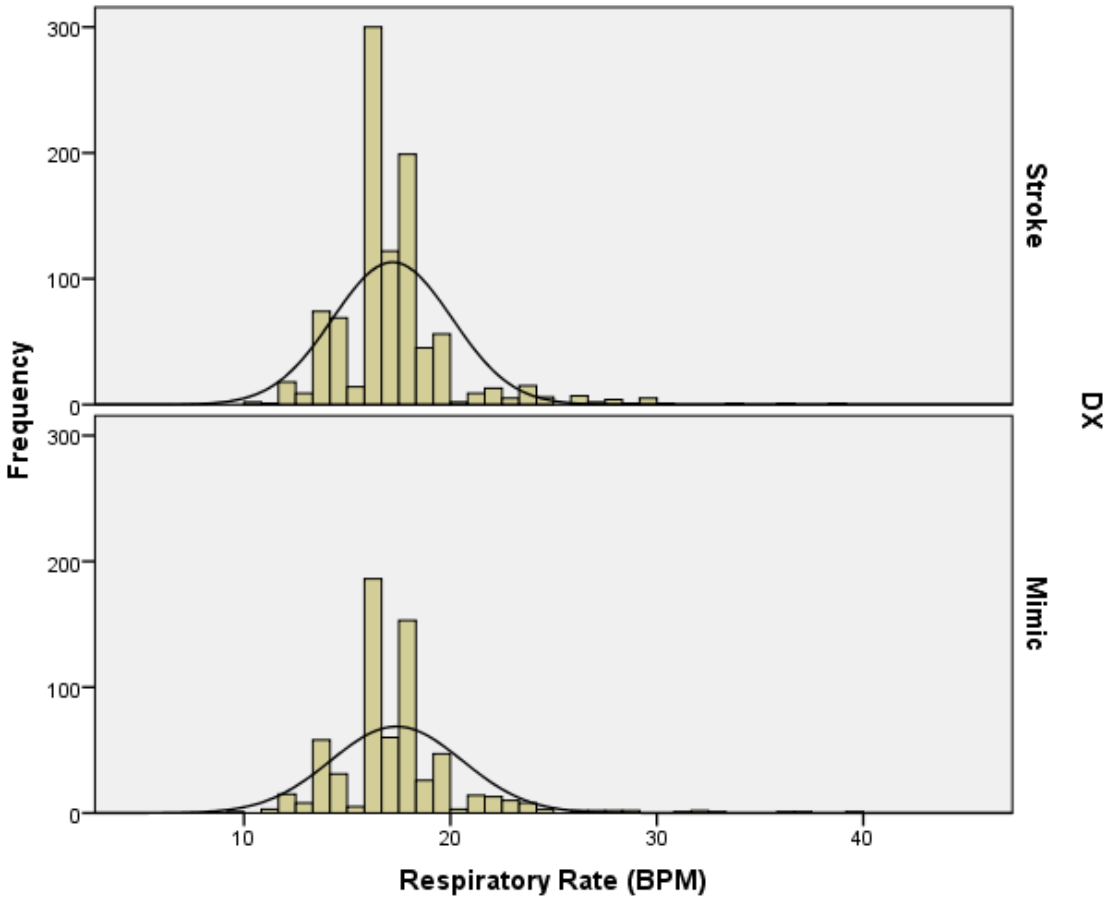

Frequency
200
150
100
50
0
Stroke
Mimic
DX
.0
5.0
10.0
15.0
20.0
25.0
30.0
BM

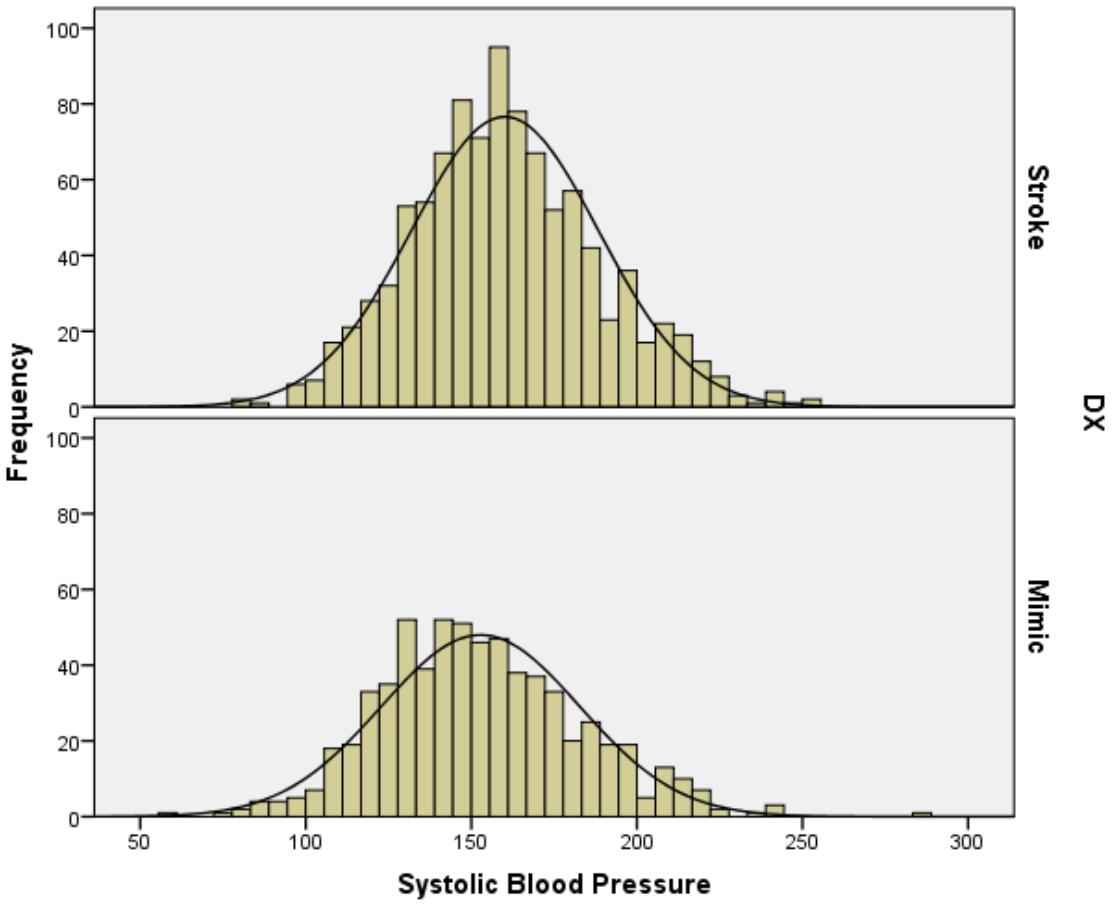

Frequency
600
500
400
300
200
100
0
Stroke
Mimic
DX
7
8
9
10
11
12
13
14
15
Glasgow Coma Scale

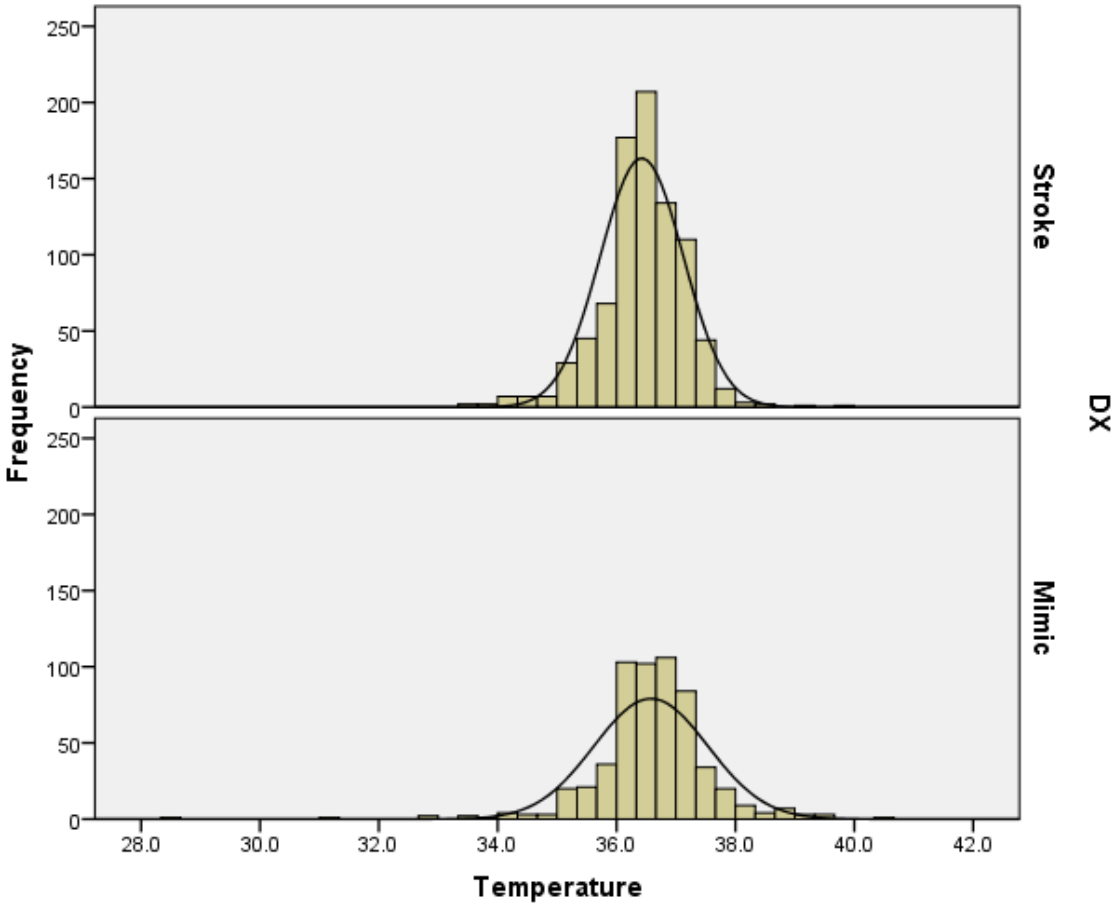

Frequency
120
100
80
60
40
20
0
Stroke
Mimic
DX
0
50
100
150
200
Heart Rate (BPM)


Frequency
600
500
400
300
200
100
0
Stroke
Mimic
DX
0
2
4
6
8
10
Pain: Numeric


Frequency
250
200
150
100
50
0
Stroke
Mimic
DX
75
80
85
90
95
100
Peripheral Oxygen Saturation (%)


Frequency
300
200
100
0
Stroke
Mimic
DX
10
20
30
40
Respiratory Rate (BPM)


Frequency
100
80
60
40
20
0
Stroke
Mimic
DX
50
100
150
200
250
300
Systolic Blood Pressure


Frequency
250
200
150
100
50
0
Stroke
Mimic
DX
28.0
30.0
32.0
34.0
36.0
38.0
40.0
42.0
Temperature

Appendix H. Focus group 1 topic guide

Paramedic Stroke Mimic (PaStraMi) Focus Groups

Topic guide: Objective 1

(These are not prescriptive, but points to be used to guide focus groups. Any topics that arise naturally during the course of the discussion should be explored.)

Introduction and housekeeping

- Researcher introduction and overview of study
- Reiterate right to withdraw/stop anytime, confidentiality, anonymity, data storage/destruction
- Any questions?
- Permission to record interview – audio and video?
- Consent

PaStraMi development (Presentation)

- Description of project
- Description of findings of systematic literature review
- Version 1 of Mimic Probability Score (MPS) based on analysis of data

The Mimic Probability Score (MPS)

- Initial thoughts on the MPS

Stroke mimics

- Stroke mimics as a general topic

Characteristics of stroke mimics

- Characteristics (demographic and clinical identified in literature review and data)

Potential application of a stroke mimic tool

- How would this type of tool work in the participants setting

Barriers/facilitators to implementing a stroke mimic tool

- What would help/hinder implementing this type of tool in prehospital care

Particular populations/conditions who may be identified or at risk

- Are there particular groups (young women) or conditions (seizures, migraines) that are of concern to participants

Any further questions

- Explain what will happen next (further focus groups, data analysis, other project activities)
- Thank all participants

Appendix I. Focus group 1 stimulus material

Paramedic Stroke Mimic (PaStraMi) Focus Groups

PaStraMi project

- Stroke Mimics (SM) present stroke-like symptoms but have a different aetiology. Approximately 30% of suspected stroke admissions are SM
- SM may bypass local hospitals to access distant hyper acute stroke units. This may be inconvenient for patients and families, inappropriate use of ambulance resources and place additional demands on stroke services
- A range of stroke identification instruments are used in pre-hospital care. These instruments are intended to identify suspected strokes in an undifferentiated population so favour sensitivity over specificity

- A systematic review of the literature indicates that
    - 29% of suspected strokes from pre-hospital care are SM
    - 27% of suspected strokes from hospital, ED and mixed settings are SM
    - 10% of suspected strokes who get thrombolysed are SM
    - Seizures/epilepsy and migraines/headaches are the most common SM

- The aim of this project is to develop a tool which identifies SM using data available in the pre-hospital setting
- The tool is intended to be applied to suspected stroke patients to inform decision making about patient destination
- Early identification of SM patients may allow transport to appropriate non-stroke care and improve healthcare resource utilisation

STEAM tool

The STEAM tool includes 5 criteria.

- **S**ystolic blood pressure <95mmHg
- **T**emperature >38.0^{o}C AND heart rate >90
- **E**pilepsy (history of) AND seizures at presentation
- **A**ge <40 years
- **M**igraine (history of) AND headache at presentation

The presence of any of these characteristics in a suspected stroke patient indicates there is a high probability of that patient being a stroke mimic.

The presence of ≥1 STEAM characteristic identifies SM with 11% (95% CI, 9-13) sensitivity, 99% (95% CI, 98-99) specificity, positive predictive value of 87% (95% CI, 78-92), negative predictive value of 62% (95% CI, 61-63)

Appendix J. Approvals for qualitative work

Health Research Authority

Mr Graham McClelland

Research Paramedic, Stroke Association Research Fellow North East Ambulance Service NHS Foundation Trust Bernicia House, Goldcrest Way Newburn Riverside Newcastle upon Tyne NE15 8NY

Email: hra.approval@nhs.net

26 January 2017

Dear Mr McClelland [redacted]

Study title:	**Input from professional stakeholder groups into the development and evaluation of a prehospital stroke mimic**
IRAS project ID:	**207285**
REC reference:	**16/HRA/6225**
Sponsor	**North East Ambulance Service NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The attached document *"After HRA Approval – guidance for sponsors and investigators"* gives detailed guidance on reporting expectations for studies with HRA Approval, including:

- Working with organisations hosting the research
- Registration of Research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to

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Your IRAS project ID is **207285**. Please quote this on all correspondence. Yours sincerely

Beverley

Mashege

de

Assessor

Email: hra.approval@nhs.net

Copy to: Ms Sonia Byers (North East Ambulance Service NHS Foundation Trust), Sponsor Contact

NIHR CRN Portfolio Applications Team

Newcastle University

Graham McClelland

Institute of Neuroscience (IoN)

Faculty of Medical Sciences

Newcastle University The Medical School Framlington Place Newcastle upon Tyne

NE2 4HH United Kingdom

FACULTY OF MEDICAL SCIENCES: ETHICS COMMITIEE

Dear Graham,

Title: Input from professional stakeholder groups into the development, evaluation and feasibility of a prehospital stroke mimic probability score

Application No: 01203/2016

Start date to end date: 01/09/2016 to 31/08/2018

On behalf of the Faculty of Medical Sciences Ethics Committee, I am writing to confirm that the ethical aspects of your proposal have been considered and your study has been given ethical approval.

The approval is limited to this project: 01203/2016. If you wish for a further approval to extend this project, please submit a re-application to the FMS Ethics Committee and this will be considered.

During the course of your research project you may find it necessary to revise your protocol. Substantial changes in methodology, or changes that impact on the interface between the researcher and the participants must be considered by the FMS Ethics Committee, prior to implementation. *

At the close of your research project please report any adverse events that have occurred and the actions that were taken to the FMS Ethics Committee.*

Best wishes,

Yours sincerely

Kimberley Sutherland

On behalf of Faculty Ethics Committee

cc.

Professor Daniel Nettle,Chair of FMS Ethics Committee Ms Lois Neal, Assistant Registrar (Research Strategy)

*Please refer to the latest guidance available on the internal Newcastle web-site.

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Appendix K. Suspected stroke patients transported to Newcastle Hospitals

Suspected stroke patients transported to Newcastle Hospitals

There were 1,000 suspected stroke patients, including 38% SM, transported by NEAS to NUTH within the study timeframe.

Patient Selection

The process of identifying the suspected stroke patients transported by NEAS to NUTH is shown in figure AP11.1.

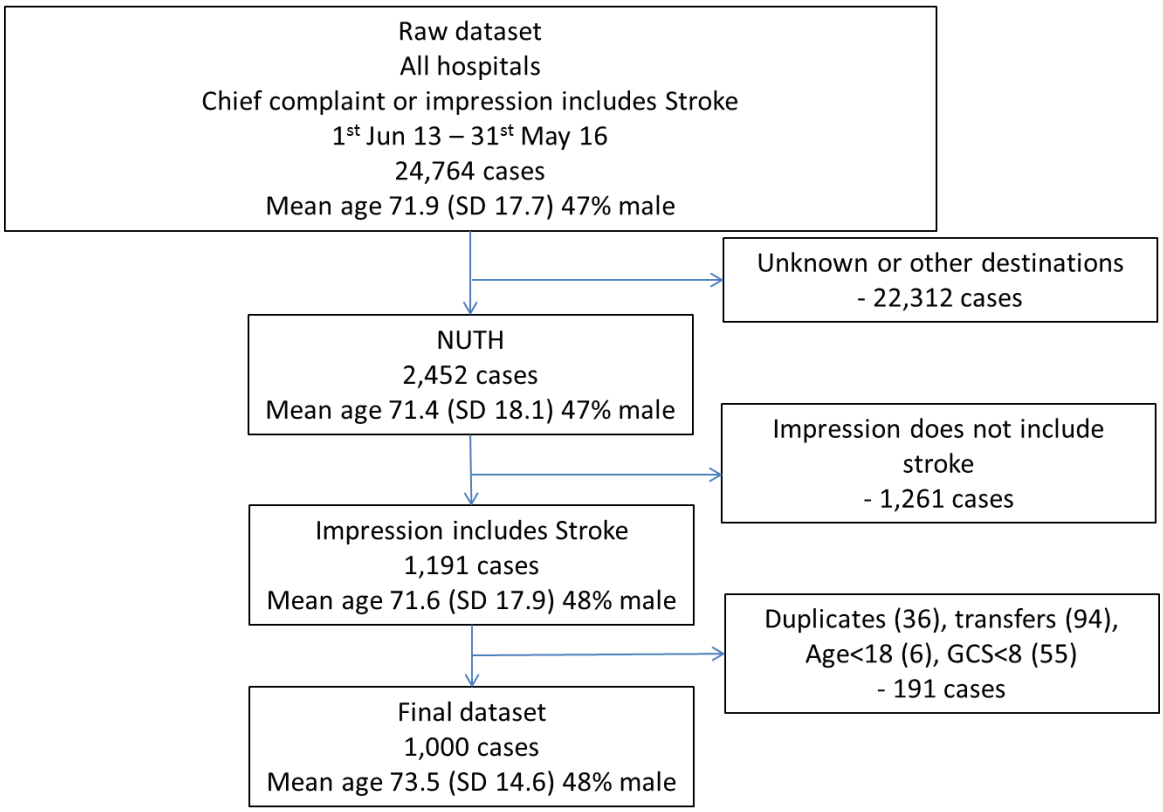


Figure AP11.1. Identification of NEAS suspected stroke patients transported to NUTH

Patient discharge diagnoses

From the total cohort of 1,000 suspected stroke patients 527 (53%) were identified as stroke patients using SSNAP. The remaining 473 suspected stroke patients who were not positively matched in the SSNAP data were searched for using the NUTH electronic record system (HES).

- 39 patients were identified as TIA (ICD-10 codes G458 and G459) based on NUTH HES records.

- 52 patients were identified as stroke based on NUTH HES records including diagnostic codes I61, I63 and I64.
- 306 patients had a SM ICD-10 diagnosis.
- 76 patients were unable to be linked with either SSNAP or HES. These patients were all assumed to be SM.

Combining these figures results in 618 (62%) stroke patients and 382 (38%) SM patients.

Assumed SM patients

SM patients were identified (n=382) by either confirmed non-stroke diagnosis (n=306 including any ICD-10 code other than I61, I63, I64 or TIA codes G458 and 459) in NUTH HES system or assumed (n=76) based on inability to match with either SSNAP or HES.

The patients assumed to be SM (n=76) were compared with the patients with a confirmed SM diagnosis.

Table AP11.1. Comparison of NUTH patients with confirmed SM diagnosis versus assumed SM diagnosis

Diagnosis	Age (mean, SD)	Gender (% Male)
Confirmed (n=306)	71.1 (16.2)	44
Assumed (n=76)	68.5 (21.1)	41

The two groups of SM patients were not significantly different in age (independent samples t-test, p=0.323) or gender (chi square test, p=0.565).

Stroke mimic diagnoses

One hundred and thirty-eight different ICD-10 diagnostic codes were recorded for the 306 patients with a confirmed SM diagnosis.

The ICD-10 based SM diagnoses are displayed in table AP11.2.

Table AP11.2 Most frequent ICD-10 diagnoses recorded for NUTH SM patients		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
R298	Other symptoms and signs involving the nervous and musculoskeletal systems	20 (7%)
N390	Urinary tract infection, site not specified	17 (6%)
R55X	Syncope and collapse	15 (5%)
R568	Convulsions, not elsewhere classified	14 (5%)
R51X	Headache	10 (3%)
G439	Migraine, unspecified	8 (3%)
R410	Disorientation, unspecified	8 (3%)
J181	Lobar pneumonia, unspecified organism	7 (2%)
C793	Secondary malignant neoplasm of brain and cerebral meninges	5 (2%)
F059	Delerium, unspecified	5 (2%)
G409	Epilepsy, unspecified	5 (2%)
J22X	Unspecified acute lower respiratory infection	5 (2%)
R202	Paresthesia of skin	5 (2%)
G819	Hemiplegia, unspecified affecting unspecified side	4 (1%)
I620	Nontraumatic subdural hemorrhage	4 (1%)
J690	Pneumonitis due to inhalation of food and vomit	4 (1%)
R208	Other disturbances of skin sensation	4 (1%)
R478	Other speech disturbances	4 (1%)
S0650	Traumatic subdural hemorrhage	4 (1%)
C349	Malignant neoplasm of unspecified part of unspecified bronchus or lung	3 (1%)
C711	Malignant neoplasm of frontal lobe	3 (1%)
E86X	Volume depletion	3 (1%)
F419	Anxiety disorder, unspecified	3 (1%)
G510	Bell's palsy	3 (1%)
I629	Nontraumatic intracranial hemorrhage, unspecified	3 (1%)
I951	Orthostatic hypotension	3 (1%)

Table AP11.2 Most frequent ICD-10 diagnoses recorded for NUTH SM patients cont.		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
R296	Repeated falls	3 (1%)
Other	Other conditions with less than 1% (n=3) prevalence	134 (44%)

The ICD-10 codes were summarised using Clinical Classification Software (CCS) codes as used earlier in chapters 1.2 and 1.4. The most frequent SM diagnoses represented using level 2 CCS codes are shown in table AP11.3.

Table AP11.3 NUTH SM diagnoses displayed using level 2 CCS codes		
CCS level 2 code	**CCS description**	**Number (%) of patients**
6.9	Other nervous system disorders	28 (9%)
6.4	Epilepsy; convulsions	27 (9%)
13.8	Other connective tissue disease	25 (8%)
6.5	Headache; including migraine	19 (6%)
10.1	Diseases of the urinary system	19 (6%)
7.3	Cerebrovascular disease	18 (6%)
17.1	Symptoms; signs; and ill-defined conditions	16 (5%)
8.1	Respiratory infections	10 (3%)
2.11	Cancer; other primary	8 (3%)
7.2	Diseases of the heart	8 (3%)
7.4	Diseases of arteries; arterioles; and capillaries	8 (3%)
Unknown	Unknown	8 (3%)
8.8	Other lower respiratory disease	7 (2%)
2.12	Secondary malignancies	6 (2%)
2.3	Cancer of bronchus; lung	6 (2%)
5.11	Alcohol-related disorders	6 (2%)
5.4	Delirium dementia and amnestic and other cognitive disorders	6 (2%)

Table AP11.3 NUTH SM diagnoses displayed using level 2 CCS codes cont.		
CCS level 2 code	**CCS description**	**Number (%) of patients**
2.14	Neoplasms of unspecified nature or uncertain behavior	5 (2%)
3.8	Fluid and electrolyte disorders	5 (2%)
6.3	Paralysis	5 (2%)
16.4	Intracranial injury	5 (2%)
2.16	Benign neoplasms	4 (1%)
8.4	Aspiration pneumonitis; food/vomitus	4 (1%)
5.2	Anxiety disorders	3 (1%)
6.6	Coma; stupor; and brain damage	3 (1%)
6.7	Eye disorders	3 (1%)
16.11	Poisoning	3 (1%)
Other	Other conditions with less than 1% (n=3) prevalence	41 (13%)

The CCS codes were combined into level 1 CCS codes to show broader clinical groupings as shown in table AP11.4.

Table AP11.4 NUTH SM diagnoses displayed using level 1 CCS codes		
CCS1 code	**CCS code description**	**Number (%) of patients**
1	Infectious and parasitic diseases	2 (1%)
2	Neoplasms	30 (10%)
3	Endocrine; nutritional; and metabolic diseases and immunity disorders	9 (3%)
4	Diseases of the blood and blood-forming organs	1 (<1%)
5	Mental Illness	18 (6%)
6	Diseases of the nervous system and sense organs	90 (29%)
7	Diseases of the circulatory system	34 (11%)
8	Diseases of the respiratory system	23 (8%)

Table AP11.4 NUTH SM diagnoses displayed using level 1 CCS codes cont.		
CCS1 code	**CCS code description**	**Number (%) of patients**
9	Diseases of the digestive system	9 (3%)
10	Diseases of the genitourinary system	19 (6%)
12	Diseases of the skin and subcutaneous tissue	1 (<1%)
13	Diseases of the musculoskeletal system and connective tissue	28 (9%)
16	Injury and poisoning	17 (6%)
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	17 (6%)
18	Residual codes; unclassified	8 (3%)

The NUTH SM diagnoses are graphically displayed in figure AP11.2 with figure 1.2.3 from the literature review repeated below for comparison.

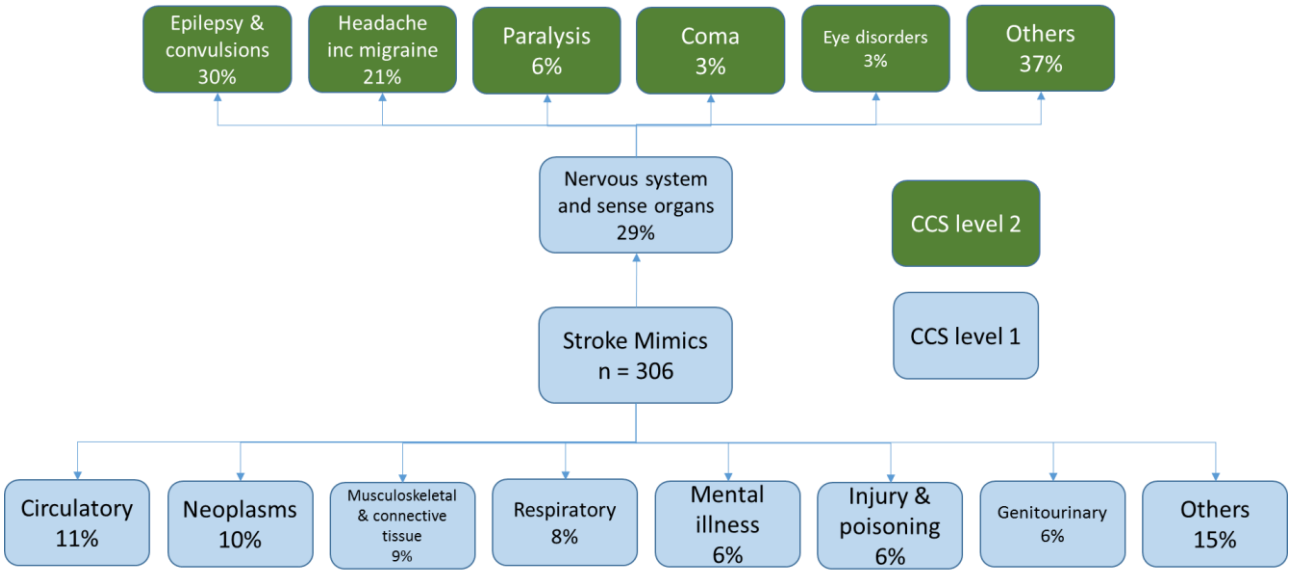


Figure AP11.2 NUTH SM diagnoses summarised using CCS codes

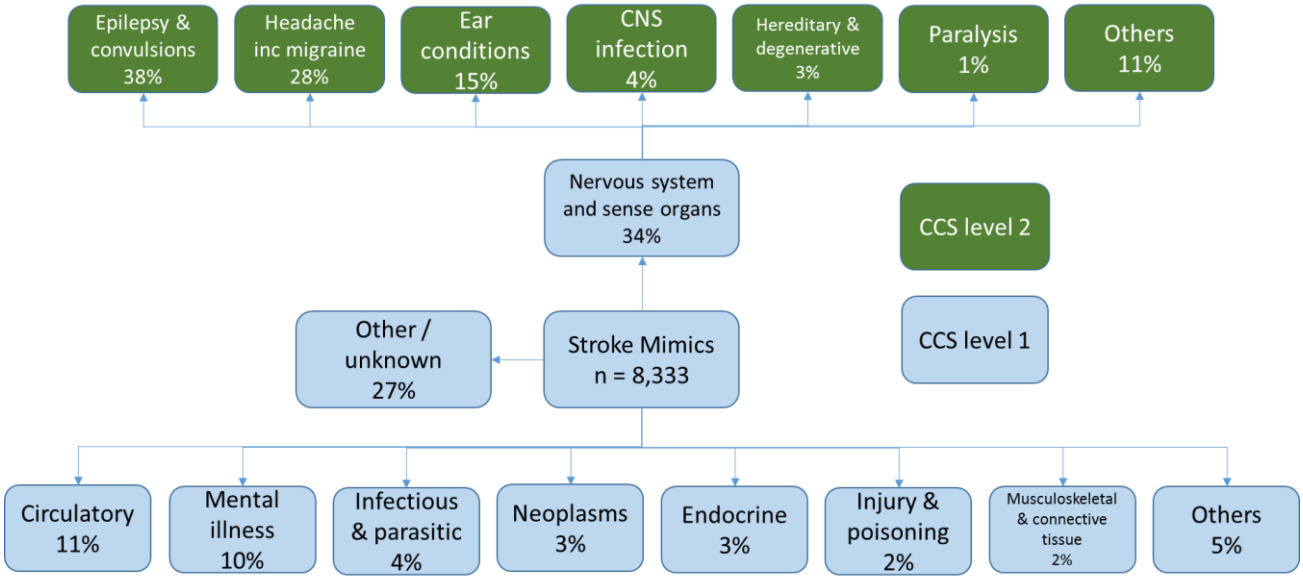


Figure 1.2.3 Taxonomy of SM using CCS codes (repeated from chapter 1.2)

Patient characteristics

The demographics of the NUTH suspected stroke cohort are displayed in table AP11.5. 100% of patients had a gender recorded. One patient had no age documented but was recorded as an adult so was included.

Table AP11.5 Demographics of NEAS suspected stroke patients transported to NUTH reported by discharge diagnosis

	Total sample	Stroke	SM	P value
Number patients	1,000	618	382	-
Mean age (SD)	73.5 (14.6)	75.3 (12.8)	70.8 (16.9)	<0.001
Gender (% male)	48%	50%	46%	0.060

The mean age for males in the NUTH cohort was 70.9 (stroke 71.9, SM 69.1). The mean age for females in the NUTH cohort was 75.9 (stroke 78.6, SM 72.1).

Physiological observations

The physiological observations recorded on suspected stroke patients transported to NUTH hospitals are displayed in table AP11.6 below.

Table AP11.6. Physiological observations in NEAS data on suspected stroke patients transported to NUTH split by final diagnosis				
Physiological observations	**% of patients with observation documented**	**Stroke (mean, SD)**	**SM (mean, SD)**	**P value**
BM (mmol/l)	96%	7.4 (2.9)	7.4 (3.1)	0.992
GCS	100%	14 (1.8)	14 (2.0)	0.176
Heart rate	99%	83 (18.9)	85 (19.5)	0.085
Irregular pulse	96%	25%	15%	<0.001
Pain (0-10)	63%	0.3 (1.0)	0.7 (1.8)	0.002
SaO2	99%	96 (2.2)	96 (4.4)	0.048
Respiratory rate	100%	17 (3.1)	17 (3.1)	0.560
SBP (mmHg)	99%	163 (29.1)	155 (29.6)	<0.001
DBP (mmHg)	99%	90 (17.4)	88 (18.1)	0.045
Temperature (Celsius)	86%	36.5 (0.6)	36.5 (0.8)	0.804

Past medical history

The characteristics of suspected stroke patients transported by NEAS to NUTH hospitals are shown in table AP11.7 below.

Table AP11.7 Past medical history of NEAS suspected stroke patients transported to NUTH reported by final diagnosis				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
PMH Alcohol misuse	18 (2%)	6 (1%)	12 (3%)	0.012
PMH Angina	79 (8%)	48 (8%)	31 (8%)	0.843
PMH Diabetes	171 (17%)	121 (20%)	50 (13%)	0.008
PMH Epilepsy	50 (5%)	19 (3%)	31 (8%)	<0.001

Table AP11.7 Past medical history of NEAS suspected stroke patients transported to NUTH reported by final diagnosis cont.				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
PMH Heart failure	25 (3%)	18 (3%)	7 (2%)	0.288
PMH High cholesterol	144 (14%)	95 (15%)	49 (13%)	0.265
PMH Hypertension	305 (30%)	215 (35%)	90 (24%)	<0.001
PMH MI	100 (10%)	64 (10%)	36 (9%)	0.633
PMH Migraine	13 (1%)	5 (1%)	8 (2%)	0.081
PMH Smoking	19 (2%)	13 (2%)	6 (2%)	0.549
PMH Stroke	257 (26%)	142 (23%)	115 (30%)	0.012
PMH TIA	161 (16%)	101 (16%)	60 (16%)	0.790

Clinical signs and symptoms

The signs and symptoms recorded by the paramedics are displayed below.

Table AP11.8 NEAS observations on suspected stroke patients transported to NUTH reported by discharge diagnosis				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
Abnormal gait	72 (7%)	53 (9%)	19 (5%)	0.032
AF*	102 (10%)	75 (12%)	27 (7%)	0.01
Alcohol/Drug use reported	35 (4%)	12 (2%)	23 (6%)	0.001
Altered Sensation (FT)*	96 (10%)	47 (8%)	49 (13%)	0.006
Arm weakness*	642 (64%)	440 (71%)	202 (53%)	<0.001

Table AP11.8 NEAS observations on suspected stroke patients transported to NUTH reported by discharge diagnosis cont.

	Patients with condition (% of total patients)	Stroke (% of stroke patients with condition)	SM (% of SM patients with condition)	P value
Chest pain	5 (1%)	2 (<1%)	3 (1%)	0.315
Confusion	290 (29%)	163 (26%)	127 (33%)	0.02
Dizziness	68 (7%)	35 (6%)	33 (9%)	0.069
Eye issues (FT)*	69 (7%)	46 (7%)	23 (6%)	0.389
Facial droop or weakness	544 (54%)	372 (60%)	172 (45%)	<0.001
FAST +ve*	535 (54%)	360 (58%)	175 (46%)	<0.001
Floppy	44 (4%)	29 (5%)	15 (4%)	0.566
General weakness	178 (18%)	95 (15%)	83 (22%)	0.011
Headache	203 (20%)	112 (18%)	91 (24%)	0.029
Leg weakness*	458 (46%)	327 (53%)	131 (34%)	<0.001
Nausea or vomiting*	113 (11%)	63 (10%)	50 (13%)	0.16
Neck Stiffness	13 (1%)	7 (1%)	6 (2%)	0.552
Seizures	31 (3%)	3 (1%)	28 (7%)	<0.001
Speech symptoms	679 (68%)	453 (73%)	226 (59%)	<0.001
Syncope	11 (1%)	3 (1%)	8 (2%)	0.018
Tremors	22 (2%)	11 (2%)	11 (3%)	0.249
Unconscious	38 (4%)	14 (2%)	24 (6%)	0.001
Visual disturbances*	75 (8%)	39 (6%)	36 (9%)	0.069

*The same criteria for these characteristics was used as documented in chapter 1.4

Paramedic documentation of impression

Paramedic impression was examined to see if it related to discharge diagnosis. Impression was grouped into three distinct categories:

1. Impression = stroke as only suspected diagnosis.
2. Impression = stroke and TIA documented as only diagnoses.
3. Impression = stroke included amongst multiple differential diagnoses.

These three categories of impression were then compared with hospital discharge diagnoses.

Table AP11.9 Paramedic impression and discharge diagnoses - NUTH			
Impression	**Total patients**	**Stroke**	**SM**
Stroke only	758	515 (68%)	243 (32%)
Stroke and TIA	80	45 (56%)	35 (44%)
Stroke plus others	162	58 (36%)	104 (64%)

The stroke plus other impression category included stroke plus a median of 1 additional impressions (range 1-6, IQR 1-2). Stroke patients with impression of 'stroke plus other' had 25 different impressions documented in addition to stroke. SM patients with impression 'stroke plus other' had 31 different impressions documented in addition to stroke.

Appendix L. Suspected stroke patients transported to North Tees Hospitals

Suspected stroke patients transported to North Tees Hospitals

There were 1,147 suspected stroke patients, including 45% SM, transported by NEAS to NTEES within the study timeframe.

Patient Selection

The process of identifying suspected stroke patients (n=1,147) transported by NEAS to NTEES is shown in figure AP12.1.

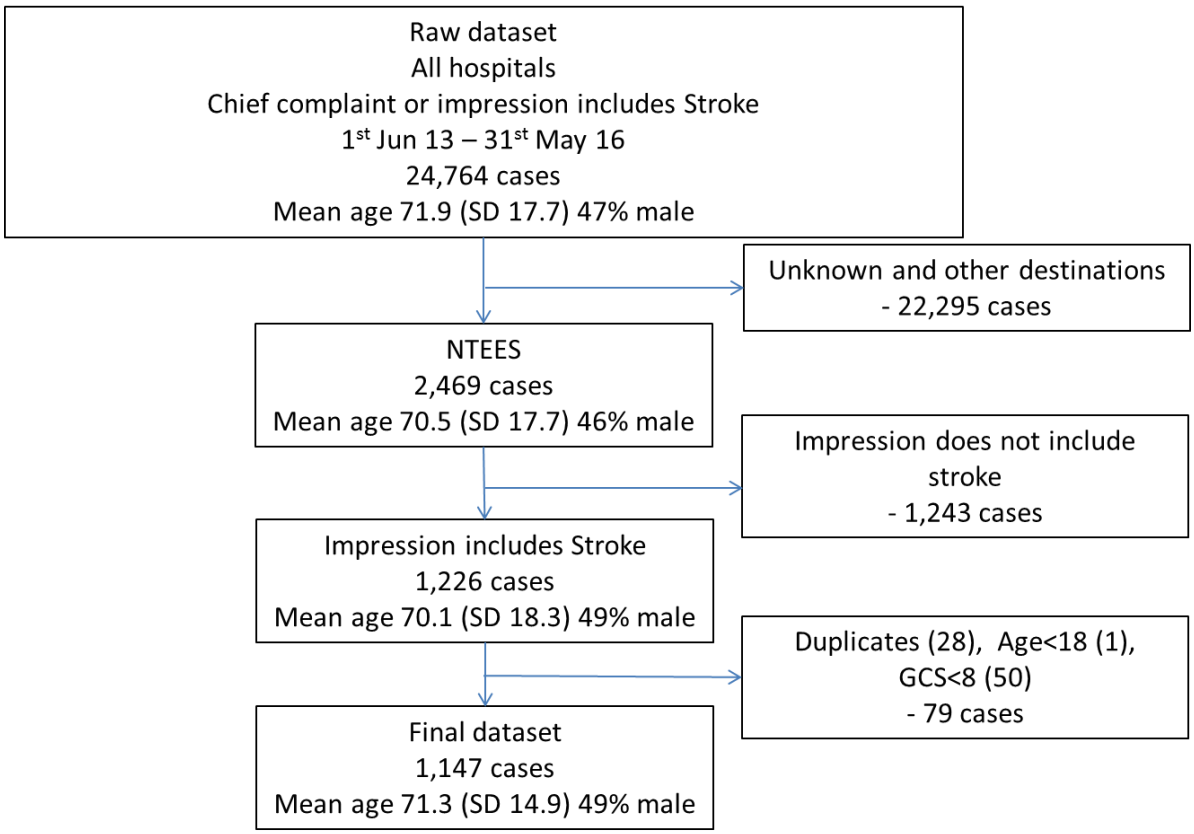


Figure AP12.1. Identification of NEAS suspected stroke patients transported to NTEES

Final patient diagnoses

From the total cohort of 1,147 suspected stroke patients 547 (48%) were identified as stroke patients using SSNAP. The remaining 600 suspected stroke patients who were not positively matched in the SSNAP data were searched for using the NTEES electronic record system (HES).

- 41 patients were identified as TIA (ICD-10 codes G458 and G459) based on NTEES HES records.

- 45 patients were identified as stroke based on NTEES HES records including diagnostic codes I61, I63 and I64.
- 158 patients had a SM ICD-10 diagnosis.
- 356 patients were unable to be linked with either SSNAP or HES. These patients were all assumed to be SM.

Combining these figures results in 633 (55%) stroke patients and 514 (45%) SM patients.

Assumed SM patients

SM patients were identified (n=514) by either confirmed non-stroke diagnosis (n=158 including any ICD-10 code other than I61, I63, I64 or TIA codes G458 and 459) in NTEES HES system or assumed (n=356) based on inability to match with either SSNAP or HES.

The patients assumed to be SM (n=356) were compared with the patients with a confirmed SM diagnosis.

Table AP12.1. Comparison of NTEES patients with confirmed SM diagnosis versus assumed SM diagnosis

Diagnosis	Age (mean, SD)	Gender (% Male)
Confirmed (n=158)	68.0 (16.4)	49
Assumed (n=356)	68.2 (16.6)	49

The two groups of SM patients were not significantly different in age (independent samples t-test, p=0.917) or gender (chi square test, p=0.965).

Stroke mimic diagnoses

Seventy different ICD-10 diagnostic codes were recorded for the 158 patients with a confirmed SM diagnosis.

The ICD-10 based SM diagnoses are displayed in table AP12.2.

Table AP12.2. Most frequent ICD-10 diagnoses recorded for NTEES SM patients		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
N390	Urinary tract infection, site not specified	12 (8%)
R55X	Syncope and collapse	12 (8%)
M628	Other specified disorders of muscle	10 (6%)
R568	Convulsions, not elsewhere classified	10 (6%)
G510	Bell's palsy	8 (5%)
G409	Epilepsy, unspecified	6 (4%)
G431	Migraine with aura	6 (4%)
G819	Hemiplegia, unspecified affecting unspecified side	5 (3%)
R51X	Headache	5 (3%)
J189	Pneumonia, unspecified organism	4 (3%)
R208	Other disturbances of skin sensation	4 (3%)
J181	Lobar pneumonia, unspecified organism	3 (2%)
J22X	Unspecified acute lower respiratory infection	3 (2%)
A084	Viral intestinal infection, unspecified	2 (1%)
A099	Gastroenteritis and colitis of unspecified origin	2 (1%)
C793	Secondary malignant neoplasm of brain and cerebral meninges	2 (1%)
F059	Delerium, unspecified	2 (1%)
F100	Mental and behavioural disorders due to use of alcohol: Acute intoxication	2 (1%)
G439	Migraine, unspecified	2 (1%)
I629	Nontraumatic intracranial hemorrhage, unspecified	2 (1%)
I951	Orthostatic hypotension	2 (1%)
I959	Hypotension, unspecified	2 (1%)
M4782	Other spondylosis cervical region	2 (1%)
R073	Other chest pain	2 (1%)
R296	Repeated falls	2 (1%)
R470	Aphasia	2 (1%)
R478	Other speech disturbances	2 (1%)

Table AP12.2. Most frequent ICD-10 diagnoses recorded for NTEES SM patients cont.		
ICD-10 Code	**ICD-10 description**	**Number (%) of patients**
Other	Other conditions with less than 1% (n=2) prevalence	42 (27%)

The ICD-10 codes were summarised using CCS codes. The most frequent SM diagnoses represented using level 2 CCS codes are shown in table AP12.3.

Table AP12.3 NTEES SM diagnoses displayed using level 2 CCS codes		
CCS level 2 code	**CCS description**	**Number (%) of patients**
6.9	Other nervous system disorders	23 (15%)
6.4	Epilepsy; convulsions	18 (11%)
13.8	Other connective tissue disease	15 (9%)
6.5	Headache; including migraine	14 (9%)
10.1	Diseases of the urinary system	13 (8%)
17.1	Symptoms; signs; and ill-defined conditions	12 (8%)
8.1	Respiratory infections	7 (4%)
7.4	Diseases of arteries; arterioles; and capillaries	6 (4%)
6.3	Paralysis	5 (3%)
7.2	Diseases of the heart	4 (3%)
9.1	Intestinal infection	4 (3%)
5.11	Alcohol-related disorders	3 (2%)
5.4	Delirium dementia and amnestic and other cognitive disorders	3 (2%)
7.3	Cerebrovascular disease	3 (2%)
8.8	Other lower respiratory disease	3 (2%)
1.3	Viral infection	2 (1%)
2.12	Secondary malignancies	2 (1%)
3.8	Fluid and electrolyte disorders	2 (1%)
6.2	Hereditary and degenerative nervous system conditions	2 (1%)

Table AP12.3 NTEES SM diagnoses displayed using level 2 CCS codes cont.		
CCS level 2 code	**CCS description**	**Number (%) of patients**
13.3	Spondylosis; intervertebral disc disorders; other back problems	2 (1%)
16.2	Fractures	2 (1%)
Other	Other conditions with less than 1% (n=2) prevalence	13 (8%)

The CCS codes were combined into level 1 CCS codes to show broader clinical groupings as shown in table AP12.4.

Table AP12.4. NTEES SM diagnoses displayed using level 1 CCS codes		
CCS1 code	**CCS code description**	**Number (%) of patients**
1	Infectious and parasitic diseases	3 (2%)
2	Neoplasms	4 (3%)
3	Endocrine; nutritional; and metabolic diseases and immunity disorders	2 (1%)
4	Diseases of the blood and blood-forming organs	1 (1%)
5	Mental Illness	7 (4%)
6	Diseases of the nervous system and sense organs	65 (41%)
7	Diseases of the circulatory system	13 (8%)
8	Diseases of the respiratory system	12 (8%)
9	Diseases of the digestive system	4 (3%)
10	Diseases of the genitourinary system	13 (8%)
12	Diseases of the skin and subcutaneous tissue	2 (1%)
13	Diseases of the musculoskeletal system and connective tissue	17 (11%)
16	Injury and poisoning	3 (2%)
17	Symptoms; signs; and ill-defined conditions and factors influencing health status	12 (8%)

The NTEES SM diagnoses are graphically displayed in figure AP12.2 with figure 1.2.3 from the systematic review repeated below for comparison.

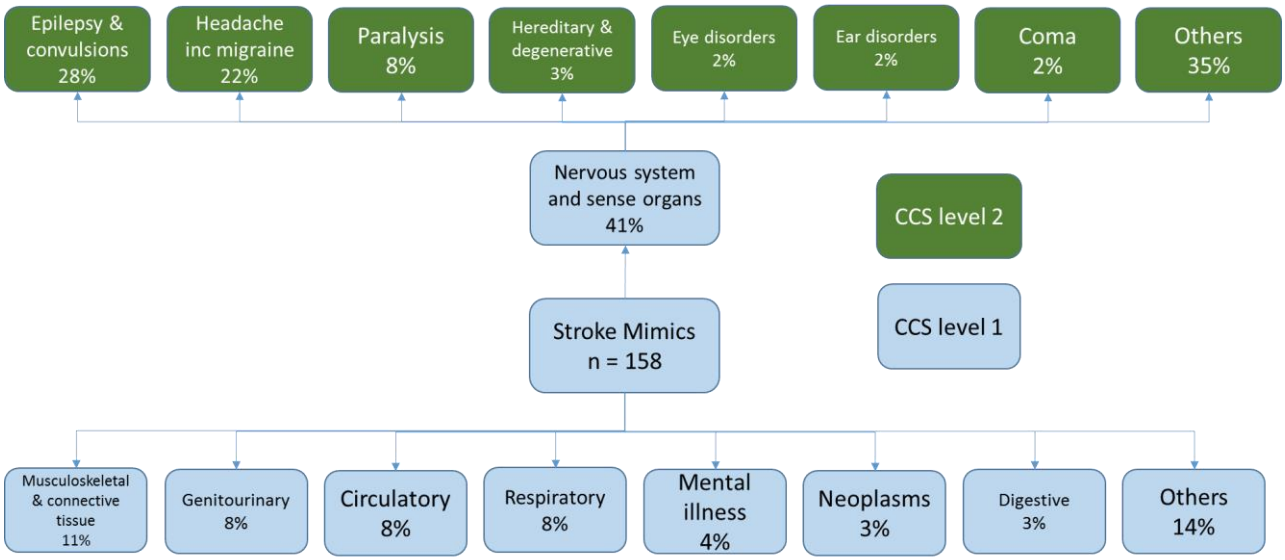


Figure AP12.2. NTEES SM diagnoses summarised using CCS codes

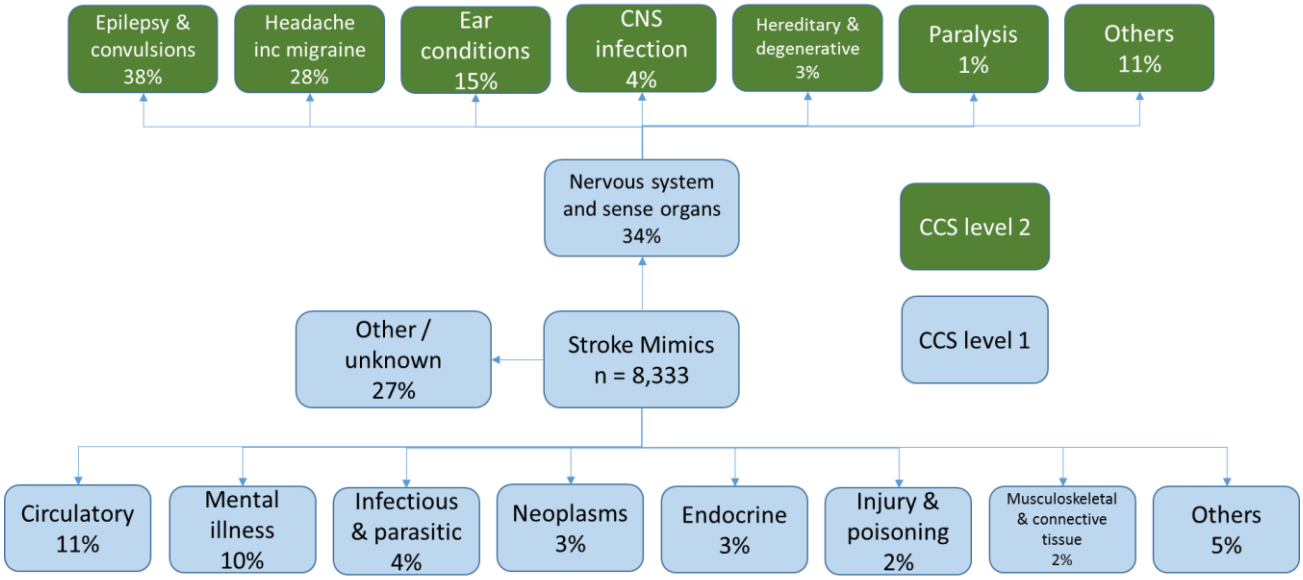


Figure 1.2.3 Taxonomy of SM using CCS codes (repeated from chapter 1.2)

Patient characteristics

The demographics of the NTEES sample are displayed below. 100% of patients had a gender recorded. Seventeen patient had no age documented but were recorded as adults so were included.

Table AP12.5. Demographics of NEAS suspected stroke patients transported to NTEES split by final diagnosis				
	Total sample	**Stroke**	**SM**	**P value**
Number patients	1,147	633	514	-
Mean age (SD)	71.3 (14.9)	73.8 (13.0)	68.1 (16.5)	<0.001
Gender (% male)	49%	49%	49%	0.982

The mean age for males in the NTEES cohort was 69.2 (stroke 70.6, SM 67.5). The mean age for females in the NTEES cohort was 73.3 (stroke 77.1, SM 68.7).

Physiological observations

The physiological observations recorded on suspected stroke patients transported to NTEES hospitals are displayed in table AP12.6 below.

Table AP12.6. Physiological observations in NEAS data on suspected stroke patients transported to NTEES split by final diagnosis				
Physiological observations	**% of patients with observation documented**	**Stroke (mean, SD)**	**SM (mean, SD)**	**P value**
BM (mmol/l)	96%	7.7(2.9)	7.6 (2.9)	0.489
GCS	100%	14 (1.7)	14 (1.7)	0.047
Heart rate	99%	83 (18.5)	83 (18.3)	0.753
Irregular pulse	99%	24%	16%	<0.001
Pain (0-10)	66%	0.3 (1.2)	0.7 (1.8)	<0.001
SaO2	99%	96 (3.1)	96 (2.5)	0.352
Respiratory rate	99%	17 (3.0)	17 (2.8)	0.636
SBP (mmHg)	99%	160 (28.7)	154 (27.4)	<0.001
DBP (mmHg)	99%	88 (17.4)	88 (18.2)	0.777
Temperature (Celsius)	88%	36.4 (0.7)	36.6 (0.8)	0.003

Past medical history

The past medical history of suspected stroke patients transported by NEAS to NTEES hospitals are shown in table AP12.7 below.

Table AP12.7. Characteristics of NEAS suspected stroke patients transported to NTEES split by discharge diagnosis				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
PMH Alcohol misuse	24 (2%)	12 (2%)	12 (2%)	0.606
PMH Angina	110 (10%)	63 (10%)	47 (9%)	0.644
PMH Diabetes	184 (16%)	100 (16%)	84 (16%)	0.803
PMH Epilepsy	50 (4%)	21 (3%)	29 (6%)	0.055
PMH Heart failure	33 (3%)	23 (4%)	10 (2%)	0.089
PMH High cholesterol	243 (21%)	137 (22%)	106 (21%)	0.674
PMH Hypertension	391 (34%)	225 (36%)	166 (32%)	0.248
PMH MI	113 (10%)	63 (10%)	50 (10%)	0.899
PMH Migraine	13 (1%)	4 (1%)	9 (2%)	0.075
PMH Smoking	30 (3%)	17 (3%)	13 (3%)	0.869
PMH Stroke	290 (25%)	125 (20%)	165 (32%)	<0.001
PMH TIA	192 (17%)	81 (13%)	111 (22%)	<0.001

Clinical signs and symptoms

The signs and symptoms recorded by the paramedics are displayed below.

Table AP12.8. NEAS observation on suspected stroke patients transported to NTEES split by discharge diagnosis				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
Abnormal gait	119 (10%)	76 (12%)	43 (8%)	0.044
AF*	96 (8%)	65 (10%)	31 (6%)	0.01
Alcohol/Drug use reported	30 (3%)	11 (2%)	19 (4%)	0.039
Altered Sensation (FT)*	105 (9%)	40 (6%)	65 (13%)	<0.001
Arm weakness*	758 (66%)	460 (73%)	298 (58%)	<0.001
Chest pain	27 (2%)	12 (2%)	15 (3%)	0.256
Confusion	330 (29%)	170 (27%)	160 (31%)	0.112
Dizziness	118 (10%)	51 (8%)	67 (13%)	0.006
Eye issues (FT)*	46 (4%)	32 (5%)	14 (3%)	0.045
Facial droop or weakness	654 (57%)	385 (61%)	269 (52%)	0.004
FAST+ve*	542 (47%)	313 (49%)	229 (45%)	0.099
Floppy	60 (5%)	31 (5%)	29 (6%)	0.573
General weakness	280 (24%)	137 (22%)	143 (28%)	0.015
Headache	274 (24%)	121 (19%)	153 (30%)	<0.001
Leg weakness*	563 (49%)	349 (55%)	214 (42%)	<0.001
Nausea or vomiting*	143 (13%)	62 (10%)	81 (16%)	0.002
Neck Stiffness	26 (2%)	11 (2%)	15 (3%)	0.182
Seizures	34 (3%)	10 (2%)	24 (5%)	0.002
Speech symptoms	774 (68%)	460 (73%)	314 (61%)	<0.001
Syncope	7 (1%)	3 (1%)	4 (1%)	0.511
Tremors	34 (3%)	17 (3%)	17 (3%)	0.537
Unconscious	49 (4%)	23 (4%)	26 (5%)	0.235

Table AP12.8. NEAS observation on suspected stroke patients transported to NTEES split by discharge diagnosis cont.				
	Patients with condition (% of total patients)	**Stroke (% of stroke patients with condition)**	**SM (% of SM patients with condition)**	**P value**
Visual disturbances*	110 (10%)	51 (8%)	59 (12%)	0.05

*The same criteria for these characteristics was used as documented in chapter 1.4

Paramedic documentation of impression

Paramedic impression was examined to see if it related to final diagnosis. Impression was grouped into three distinct categories:

1. Impression = stroke as only suspected diagnosis.
2. Impression = stroke and TIA documented as only diagnoses.
3. Impression = stroke included amongst multiple differential diagnoses.

These three categories of impression were then compared with final hospital diagnoses.

Table AP12.9. Paramedic impression and discharge diagnoses - NTEES			
Impression	**Total patients**	**Stroke**	**SM**
Stroke only	872	514 (59%)	358 (41%)
Stroke and TIA	87	47 (54%)	40 (46%)
Stroke plus others	188	72 (38%)	116 (62%)

The stroke plus other impression category included stroke plus a median of 2 additional impressions (range 1-8, IQR 1-2). Stroke patients with impression of 'stroke plus other' had 25 different impressions documented in addition to stroke. SM patients with impression 'stroke plus other' had 31 different impressions documented in addition to stroke.

Appendix M. Usability testing feedback form

Paramedic Stroke Mimic (PaStraMi) Study

Feedback on mimic assessment tool

1. **What are your general thoughts on the mimic assessment tool?**

2. **How easy or difficult was it to include the mimic tool characteristics in your assessment?**

   Very difficult Difficult Neutral Easy Very Easy

3. **Did the mimic tool agree with your clinical decision making?**

   Never Rarely Sometimes Mostly Always

4. **What did you think about using the mimic tool in practice?**

5. **Are there any criteria within the tool that you think need changing?**

6. **What format do you think the tool would be most useful in?**

7. **What would be the best way to train paramedics to use this tool if it became part of normal practice?**

8. **When the tool indicated a patient may be a stroke mimic how would you have felt about not following your standard stroke protocol?**

9. **How could you see the mimic tool fitting in with your local protocols?**

10. **Is there anything else you think might be useful to the project going forward that we haven't asked about?**

Name……..

Signed…….

Date…….....

Paramedic Stroke Mimic (PaStraMi) Study

Stroke mimic assessment tool training

Background

Between 25 and 50% of suspected stroke patients admitted to hospital by ambulance turn out to be non-stroke conditions. We call these conditions stroke mimics as they present with stroke like symptoms but have a different underlying cause. This project is looking into whether paramedics can accurately identify some of these stroke mimics using the tool described below.

The tool

We have developed a simple tool that identifies some stroke mimics. The STEAM tool involves 5 characteristics that indicate a suspected stroke patient may be a stroke mimic.

1. **S**ystolic blood pressure < 95mmHg
2. **T**emperature > 38oC AND heart rate >90 bpm
3. History of **E**pilepsy AND seizures at presentation
4. **A**ge < 40 years

5. History of **M**igraine AND headache at presentation

The presence of 1 or more of these characteristics identifies around 10% of stroke mimics with around 90% accuracy.

What you need to do

We want you to document the presence or absence of these characteristics when you are attending a suspected stroke patient and consider if the patient could be a stroke mimic.

IMPORTANT - We are NOT asking you to change your treatment in any way so follow your normal stroke protocol.

We will contact you at the end of the study for some feedback on the tool and how you used it in practice.

What happens next?

If you are happy with the tool please email Graham McClelland to confirm you are happy to participate in this evaluation and start using the STEAM tool on all suspected strokes. If you are not happy with the tool please contact Graham McClelland and we will arrange face to face training or answer any questions you may have.

Contacts

Graham or Sonia can be contacted any time during the study if you have any questions or concerns.

Graham McClelland graham.mcclelland@neas.nhs.uk or on 0191 430 2244 or 0191 208 6232

If you would like to speak to someone else about the study please contact Sonia Byers (R&D Manager) Sonia.byers@neas.nhs.uk or on 0191 430 2192

Appendix O. Usability testing interview topic guide

Paramedic Stroke Mimic (PaStraMi) Study

Interview schedule: mimic evaluation

(These are not prescriptive, but points to be used to guide interviews. Any topics that arise naturally during the course of the discussion should be explored.)

Introduction and housekeeping

- Researcher introduction and overview of study
- Reiterate right to withdraw/stop anytime, confidentiality, anonymity, data storage/destruction
- Any questions?
- Permission to record interview – audio?
- Consent

PaStraMi development (Presentation)

- Description of project
- Description of findings of systematic literature review
- Development of the mimic tool

Stroke mimics

- Stroke mimics as a general topic (refer back to literature and survey data)

The Mimic Tool

- Initial thoughts on the mimic tool
- How did people find using the tool? Any tweaks or suggestions?
- Did the tool fit into participant's normal assessment and practice? Were there any issues?
- Format of the tool – would memory aids be useful?
- Particular patients where the tool was used?
  Any feedback on/from hospitals?

Barriers/facilitators to implementing the stroke mimic tool

- What would help/hinder implementing this type of tool in prehospital care
- How could we roll this out across a large area?
- Any particular training needs?

Particular populations/conditions who may be identified or at risk

- Are there particular groups (young) or conditions (seizures, migraines) that are of concern to participants

Any further questions

- Explain what will happen next (further interviews, data analysis, other project activities)
- Thank participant

Appendix P. Usability testing interview stimulus material

STEAMv1

Application to GCS8+

- 1 point for SBP<95mmHg
- 1 point for Temp>38.0^{o}C AND HR>90 BPM
- 1 point for Seizures AND PMH epilepsy
- 1 point for Age < 40 years
- 1 point for Migraine AND headache

Score 1+ = 11% sens, 99% spec, 86% PPV

STEAMv2

Application to GCS8+ and BM3+

- 1 point for SBP<90mmHg
- 1 point for Temp>38.5^{o}C AND HR>90 BPM
- 1 point for Seizures **OR** 2 points for Seizures AND PMH epilepsy
- 1 point for Age < 40 years **OR** 2 points for Age < 30 years
- 1 point for Migraine AND headache
- 1 point for FAST-ve

Score 2+ = 5% sens, 100% spec, 92% PPV

Usability testing

SBP, Temp, HR, Age all consistently recorded

Seizures commonly recorded

Headache recorded about half the time

PMH epilepsy or migraine rarely recorded

STEAM rarely recorded

Appendix Q. Focus group 3 topic guide

Paramedic Stroke Mimic (PaStraMi) Focus Groups

Topic guide: Focus group 3

Introduction and housekeeping

- Researcher introduction and overview of study
- Reiterate right to withdraw/stop anytime, confidentiality, anonymity, data storage/destruction, no right or wrong answers
- Any questions?
- Permission to record interview – audio?
- Consent

Background

Development process, lit – survey – STEAMv1 – FG – usability – refinement – STEAMv2 – modelling (handout1 – process, STEAMv1 and v2)

Topics

- STEAMv2
    - STEAMv2 criteria
    - STEAMv2 performance
    - Compare and contrast STEAMv1 and v2
        - how does STEAM1 (more SM but more stroke) compare with STEAMv2 (less of both but more accuracy)

- Pre-alerting stroke and SM patients
- Existing prehospital exclusion criteria in local practice
- Time since onset
- Telemedicine

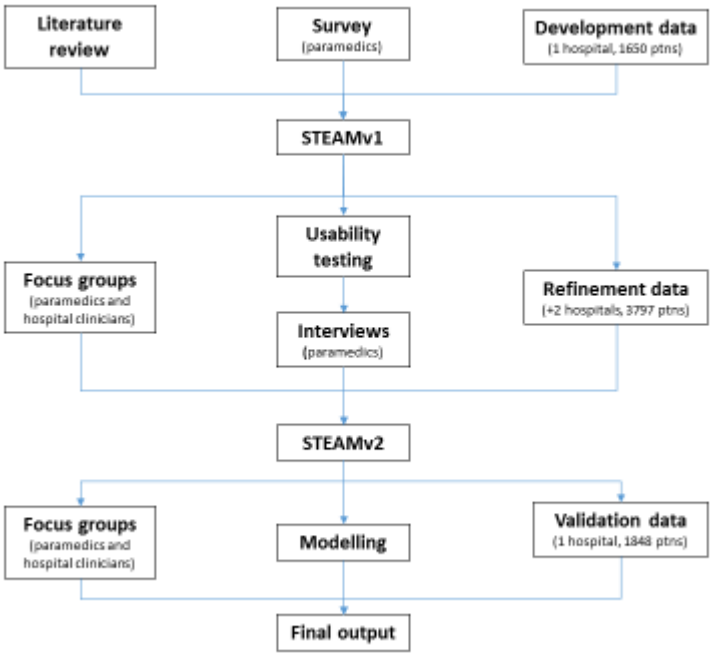
- Modelling
    - 4 domains (handout 2 – domains, outputs)
    - Chameleon rate – context
    - FP rate
    - 3 relevant groups – patients, ambulance service, stroke services
- Could this work in practice?

- What would you like to see next?

Any further questions

- Explain what will happen next
- Thank all participants

Appendix R. Focus group 3 stimulus material



STEAMv1 (any 1 point = likely SM)

- 1 point for **S**BP<95mmHg
- 1 point for **T**emp>38.0°C AND HR>90 BPM
- 1 point for Seizures AND PMH **E**pilepsy
- 1 point for **A**ge < 40 years
- 1 point for Headache AND PMH **M**igraine

STEAMv1 performance

Sensitivity 12%
Specificity 99%
PPV 84%

STEAMv2 (Age 18+, GCS 8+, BM 3+, any 2 points = likely SM)

- 1 point for **S**BP<90mmHg
- 1 point for **T**emp>38.5°C AND HR>90 BPM
- 1 point for Seizures, 2 points for Seizures AND PMH **E**pilepsy
- 1 point for Age < 40 years, 2 points for **A**ge < 30 years
- 1 point for Headache AND PMH **M**igraine
- 1 point for FAST-ve

STEAMv2 performance

Sensitivity 6%
Specificity 99%
PPV 91%

Sensitivity 6%
Specificity 99%
PPV 83%

Modelling introducing STEAMv2 into practice

Modelled 1,000 stroke patients
Assumed pre-hospital stroke recognition 79% sensitive and 60% PPV,
With 100% use of STEAMv2, 26 SM patients correctly identified, 2 stroke patients incorrectly identified
Pre-hospital PPV improves to 62%

Treatment rates and speeds
Call-to-door should be very similar (40-60 minutes)
If SM are not pre-alerted this will impact on door-to-scan times (6-146 minutes) which then impacts on door-to-needle times
Dependent on ED practice

Population disability
STEAMv2 misclassified 8 stroke ptns (inc 1xTIA) as SM in 3,797 refinement cohort – 2 were thrombolysed, 2 unknown, 4 not thrombolysed - therefore 25-50% potential missed thrombolysis rate in STEAMv2 false positives

Early access to specialist stroke services is associated with improved patient outcomes. Stroke units have limited capacity and delays in being admitted to stroke units are reported. SM occupy stroke unit beds when they could be appropriately treated elsewhere. Reducing the use of stroke unit beds by SM should enable stroke patients to access stroke units more rapidly and therefore improve patient outcomes

Workforce implications
SM account for 8-17% of HASU beds with a mean stay between 1.5-2.8 days
Reduced travel time for ambulance crews

Health economics
Admitting a SM to a general ward rather than a HASU saves £771-1,439 per patient
SSNAP estimates a missed thrombolysis opportunity as £5,800 for health and social care over 1 year
Overall care costs for stroke patients vary between £7,322 to £44,854 over 1 year

Appendix S. UK pre-hospital stroke pathways

In May 2018 stroke pathways were sourced from all ten of the UK regional ambulance services and the Northern Irish, Scottish and Welsh ambulance services to explore how representative the NEAS and NWAS pathways were and to determine if other services were already using criteria to rule out SM. Pathways were sourced from each services website or via direct contact with paramedics in each service. The results are shown in table AP19.1.

Table AP19.1. Summary of pre-hospital stroke pathways

Ambulance Service Number	Stroke identification tool	Summary of pathway	Minimum age	Time (hours)	GCS exclusion	BM (mmol/l) exclusion	Seizures excluded	Other exclusions
1a	FAST	ASU if FAST+ within 4 hours, local ED if not	NA	4	<8	<4.0	Yes	Airway, RR<10 or >30, SPO2<90, BP<90, HR<40 or
1b	FAST	<4 hours HASU, 4-48 hours HASU +/- pre-alert anticoags, >48 hours nearest ED	16+	Variable	<8	<4.0	Yes	Airway, RR<10 or >30, SPO2<90, BP<90, HR<40 or >150
2	FAST	<4.5 hours pre-alert to HASU, >4.5 hours normal driving to HASU	18+	4.5			Yes	ABC concern = local ED
3	FAST + AVVV mnemonic	Within 5 hours, conscious, pre-alert ED	NA	5	Conscious	<3.0	Yes	
4	FAST	Symptom onset <4.5 hours = thrombolysing hospital	NA	4.5				
5	FAST	Arrive at thrombolysing hospital within 5.5 hours from onset	NA	5.5		<4.0	Yes	
6	FAST	4.5-6 hours pre-alert to stroke team at hospital, otherwise normal clinical practice	18+	Variable		<4.0	Yes	
7	FAST	Symptoms<3 hours = HASU, symptoms>3 hours nearest ASU, both with pre-alert	NA	3				
8	FAST & MEND	4.5-6 hours to arrival dependent on hospital	NA	Variable		<3.5		
9	FAST	Thrombolysing hospital within 4.5 hours otherwise nearest ED	NA	4.5		Hypoglycaemia		Major ABC problem
10	FAST	Onset within 5 hours	18+	5	<11	<3.5		
11	FAST	<4.5 hours pre-alert most approrpriate ED, >4.5 hours normal drive to ED	NA	4.5		<4.0		
12	FAST inc leg weakness or vision loss <12 hours	Pre-alert to local shortest travel time HASU otherwise nearest ED with pre-alert	18+		<8		Yes	Airway, LOC, head injury, clinically unstable
13	FAST	Time critical = nearest ED, FAST+ pre-alert to recognised stroke unit	NA					

The results showed that FAST was included in all 13 pathways, which supported the results of the survey in chapter 1.2, but revealed that three services had additional screening criteria including leg weakness and posterior circulation stroke symptoms. Since this survey was conducted one service introduced BEFAST so four services now have additional screening criteria. It is unknown how these additional screening criteria impact on the SM rate and how a tool like STEAMv2 would perform in these services both of which would be valuable areas for future research.

The upper time limit for transporting a suspected stroke patient directly to specialist stroke services as a medical emergency varied between 3 and 6 hours from onset, with two services extending the time threshold to 12 and 48 hours for specific presentations.

Seizures (6 pathways) and reduced consciousness level (4 pathways) were criteria for transportation to the nearest ED instead of specialist stroke services. The blood glucose

threshold for considering hypoglycaemia varied from 3 to 4 mmol/l (8 pathways). One service (service 1) used physiological parameters e.g. respiratory rate, heart rate and blood pressure, to direct potential stroke patients to ED.

References

Abboud, M.E., Band, R., Jia, J., Pajerowski, W., David, G., Guo, M., Mechem, C.C., Messe, S.R., Carr, B.G. and Mullen, M.T. (2016) 'Recognition of stroke by EMS is associated with improvement in emergency department quality measures', *Prehospital Emergency Care*, 20(6), pp. 729-736.

Abdul-Ghani, M.A., Abdul-Ghani, T., Stern, M.P., Karavic, J., Tuomi, T., Bo, I., Defronzo, R.A. and Groop, L. (2011) 'Two-step approach for the prediction of future type 2 diabetes risk', *Diabetes Care*, 34(9), pp. 2108-12.

Adams, S.T. and Leveson, S.H. (2012) 'Clinical prediction rules', *BMJ*, 344, p. d8312.

Aiyesimoju, A.B., Osuntokun, B.O., Adeuja, A.O., Olumide, A. and Ogunseyinde, A.O. (1983) 'Misdiagnosis of stroke', *African Journal of Medicine and Medical Sciences*, 12(2), pp. 107-12.

Ali, S., Geisler, F., Ebinger, M., Kunz, A., Rozanski, M., Waldschmidt, C., Weber, J., Wendt, M., Winter, B., Schwamm, L. and Audebert, H. (2018) 'Evaluation of the Tele-Stroke Mimic Score (TM-Score) for prehospital distinction between stroke and stroke mimic patients', *Neurology*, 90(Supplement 15), p. P6.251.

Ali, S.F., Hubert, G., Switzer, J., Majersik, J., Backhaus, R., Vedala, K., Sundararaghavan, A., Shepard, L.W. and Schwamm, L. (2016) 'External validation of the telestroke mimic (TM) score for predicting stroke mimics evaluated during telestroke', *Stroke*, 47(Suppl 1), p. A118.

Ali, S.F., Singhal, A.B., Feske, S.K., Davis, L.W., Forducey, P.G., Nystrom, K., Schindler, J.L., Schlegel, S., Likosky, W.H., Solenski, N.J., Southerland, A.M. and Schwamm, L.H. (2014) 'The TeleStroke Mimic (TM) Score: A prediction rule for identifying stroke mimics evaluated in a telestroke network', *Journal of the American Heart Association*, 3(3), p. e000838.

Allen, M., Pearn, K., Villeneuve, E., Monks, T., Stein, K. and James, M. (2017) 'Feasibility of a hyper-acute stroke unit model of care across England: a modelling analysis', *BMJ Open*, 7(12), p. e018143.

Alonge, O., Barrett, C., Adams, J., Speirs, O. and Clarke, B. (2013) 'Stroke mimics in a district general hospital hyper acute stroke unit', *International Journal of Stroke*, 8(Suppl 3), pp. 1-2.

Alonso, J.V., Lopera, E.L., Fonseca, J., Lopez, A.S., Montes, Y.H. and Del Carmen Munoz Villanueva, M. (2014) 'Stroke mimics: A challenge for the emergency physician', *Resuscitation*, 85, p. S115.

Altman, D.G., Vergouwe, Y., Royston, P. and Moons, K.G.M. (2009) 'Prognosis and prognostic research: validating a prognostic model', *BMJ*, 338, p. b605.

Alves, M., Narciso, M., Miranda, A. and Fonseca, T. (2016) 'Prevalence and characterization of stroke mimics in a stroke unit', *Medicina Interna*, 23(3), p. 5.

Amarenco, P., Lavallée, P.C., Labreuche, J., Albers, G.W., Bornstein, N.M., Canhão, P., Caplan, L.R., Donnan, G.A., Ferro, J.M., Hennerici, M.G., Molina, C., Rothwell, P.M., Sissani, L.,

Školoudík, D., Steg, P.G., Touboul, P., Uchiyama, S., Vicaut, É. and Wong, L.K.S. (2016) 'One-Year risk of stroke after transient ischemic attack or minor stroke', *New England Journal of Medicine*, 374(16), pp. 1533-1542.

An, S.A., Kim, J., Kim, O.J., Kim, J.K., Kim, N.K., Song, J. and Oh, S.H. (2013) 'Limited clinical value of multiple blood markers in the diagnosis of ischemic stroke', *Clinical Biochemistry*, 46(9), pp. 710-5.

Andsberg, G., Esbjornsson, M., Olofsson, A., Lindgren, A., Norrving, B. and von Euler, M. (2017) 'PreHospital Ambulance Stroke Test - pilot study of a novel stroke test', *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 25(1), p. 37.

Ankolekar, S., Parry, R., Sprigg, N., Siriwardena, A.N. and Bath, P.M.W. (2014) 'Views of paramedics on their role in an out-of-hospital ambulance-based trial in ultra-acute stroke: Qualitative data from the rapid intervention with glyceryl trinitrate in hypertensive stroke trial (RIGHT)', *Annals of Emergency Medicine*, 64(6), pp. 640-648.

Appleton, J.P., Sprigg, N. and Bath, P.M. (2016) 'Blood pressure management in acute stroke', *Stroke and Vascular Neurology*, 1(2), pp. 72-82.

Aravind, A., Aweid, B., Jamil, S. and Kar, A. (2015) 'Mimics at a large London HASU', *International Journal of Stroke*, 10(Suppl 5), p. 53.

Arch, A.E., Weisman, D.C., Coca, S., Nystrom, K.V., Wira, C.R. and Schindler, J.L. (2016) 'Missed ischemic stroke diagnosis in the emergency department by emergency medicine and neurology services', *Stroke*, 47(3), pp. 668-673.

Artto, V., Putaala, J., Strbian, D., Meretoja, A., Piironen, K., Liebkind, R., Silvennoinen, H., Atula, S., Happola, O. and Group, H.S.T.R. (2012) 'Stroke mimics and intravenous thrombolysis', *Annals of Emergency Medicine*, 59(1), pp. 27-32.

Asaithambi, G., Castle, A.L., Sperl, M.A., Ravichandran, J., Gupta, A., Ho, B.M. and Hanson, S.K. (2017) 'Thrombolytic treatment to stroke mimic patients via telestroke', *Clinical Neurology and Neurosurgery*, 153, pp. 5-7.

Asplund, K., Karvanen, J., Giampaoli, S., Jousilahti, P., Niemela, M., Broda, G., Cesana, G., Dallongeville, J., Ducimetriere, P., Evans, A., Ferrie`res, J., Haas, B., Jorgensen, T., Tamosiunas, A., Vanuzzo, D., Wiklund, P.G., Yarnell, J., Kuulasmaa, K., Kulathinal, S. and for the MORGAM Project (2009) 'Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project', *Stroke*, 40, pp. 2319-2326.

Association of Ambulance Chief Executives and Joint Royal Colleges Ambulance Liaison Committee, J. (2016) *UK Ambulance Services Clinical Practice Guidelines 2016*. Bridgwater, UK: Class Publishing.

Austin, P.C. and Steyerberg, E.W. (2015) 'The number of subjects per variable required in linear regression analyses', *Journal of Clinical Epidemiology*, 68(6), pp. 627-636.

Ay, H., Buonanno, F., Rordorf, G., Schaefer, P., Schwamm, L., Wu, O., Gonzalez, R., Yamada, K., Sorensen, G. and Koroshetz, W. (1999) 'Normal diffusion-weighted MRI during stroke-like deficits', *Neurology*, 52(9), pp. 1784-1792.

Bannister, M. (2013) '"BM" – the biggest misnomer in diabetes clinical practice', *Journal of Diabetes Nursing*, 17(2), p. 46.

Barbour, R. (2008) *Doing focus groups*. London: Sage.

Barker, W.H., Feldt, K.S. and Feibel, J. (1984) 'Assessment of hospital admission surveillance of stroke in a metropolitan community', *Journal of Chronic Diseases*, 37(8), pp. 609-15.

Bath, P.M.W., Dixon, M., Appleton, J., Scutt, P., England, T., Foster, H., Howard, H., Jarvis, M., Montgomery, A., Pocock, S., Potter, J., Price, C., Robinson, T., Roffe, C., Siriwardena, A.N., Sprigg, N. and Wardlaw, J. (2016) 'Rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2 (RIGHT-2): Safety and efficacy of transdermal glyceryl trinitrate, a nitric oxide donor', *Emergency Medicine Journal*, 33(9), pp. e13-e14.

Bayer, A., Price, C.I., Rae, V., Duckett, J., Wood, R., Gray, J., McMeekin, P., Rodgers, H., Portas, K. and Ford, G.A. (2013) 'An observational study of patient characteristics associated with the mode of admission to acute stroke services in North East England', *PLOS ONE*, 8(10), p. e76997.

Bayer, S., Petsoulas, C., Cox, B., Honeyman, A. and Barlow, J. (2010) 'Facilitating stroke care planning through simulation modelling', *Health Informatics Journal*, 16(2), pp. 129-143.

Birenbaum, D., Bancroft, L.W. and Felsberg, G.J. (2011) 'Imaging in acute stroke', *Western Journal of Emergency Medicine*, 12(1), pp. 67-76.

Bivard, A., Levi, C., Krishnamurthy, V., McElduff, P., Miteff, F., Spratt, N.J., Bateman, G., Donnan, G., Davis, S. and Parsons, M. (2015) 'Perfusion computed tomography to assist decision making for stroke thrombolysis', *Brain*, 138(7), pp. 1919-1931.

Bone, R.C., Balk, R.A., Cerra, F.B., Dellinger, R.P., Fein, A.M., Knaus, W.A., Schein, R.M.H. and Sibbald, W.J. (1992) 'Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis', *Chest*, 101(6), pp. 1644-1655.

Brandler, E.S., Sharma, M., McCullough, F., Ben-Eli, D., Kaufman, B., Khandelwal, P., Helzner, E., Sinert, R.H. and Levine, S.R. (2015) 'Prehospital stroke identification: Factors associated with diagnostic accuracy', *Journal of Stroke and Cerebrovascular Diseases*, 24(9), pp. 2161-2166.

Bray, J.E., Martin, J., Cooper, G., Barger, B., Bernard, S. and Bladin, C. (2005) 'Paramedic identification of stroke: Community validation of the Melbourne ambulance stroke screen', *Cerebrovascular Diseases*, 20(1), pp. 28-33.

Brotons, A.A., Motola, I., Rivera, H.F., Soto, R.E., Schwemmer, S. and Issenberg, S.B. (2012) 'Correlation of the Miami Emergency Neurologic Deficit (MEND) exam performed in the field by paramedics with an abnormal NIHSS and final diagnosis of stroke for patients airlifted from the scene.', *Stroke*, 43(Suppl 1), p. A3468.

Brott, T., Adams Jr., H.P., Olinger, C.P., Marler, J.R., Barsan, W.G., Biller, J., Spilker, J., Holleran, R., Eberle, R., Hertzberg, V., Rorick, M., Moomaw, C.J. and Walker, M. (1989) 'Measurements of acute cerebral infarction: a clinical examination scale', *Stroke*, 20(7), pp. 864-70.

Brunser, A., Illanes, S., Lavados, P., Muñoz, P., Cárcamo, D., Hoppe, A., Olavarria, V., Delgado, I. and Díaz, V. (2013) 'Exclusion criteria for intravenous thrombolysis in stroke mimics: an observational study', *Journal of Stroke & Cerebrovascular Diseases*, 22(7), pp. 1140-1145.

Burges Watson, D.L., Sanoff, R., Mackintosh, J.E., Saver, J.L., Ford, G.A., Price, C., Starkman, S., Eckstein, M., Conwit, R., Grace, A. and Murtagh, M.J. (2012) 'Evidence from the scene: Paramedic perspectives on involvement in out-of-hospital research', *Annals of Emergency Medicine*, 60(5), pp. 641-650.

Bustamante, A., Lopez-Cancio, E., Pich, S., Penalba, A., Giralt, D., Garcia-Berrocoso, T., Ferrer-Costa, C., Gasull, T., Hernandez-Perez, M., Millan, M., Rubiera, M., Cardona, P., Cano, L., Quesada, H., Terceno, M., Silva, Y., Castellanos, M., Garces, M., Reverte, S., Ustrell, X., Mares, R., Baiges, J.J., Serena, J., Rubio, F., Salas, E., Davalos, A. and Montaner, J. (2017) 'Blood biomarkers for the early diagnosis of stroke: The Stroke-Chip Study', *Stroke*, 48(9), pp. 2419-2425.

Callaham, M. (1997) 'Quantifying the scanty science of prehospital emergency care', *Annals of Emergency Medicine*, 30(6), pp. 785-90.

Cerebrotech Medical Systems (2018) *Cerebrotech Medical Systems*. Available at: http://www.cerebrotechmedical.com/eu.php (Accessed: 06/08/2018).

Chang, J., Teleb, M., Yang, J., Alderazi, Y., Chapple, K., Frey, J. and Restrepo, L. (2012) 'A model to prevent fibrinolysis in patients with stroke mimics', *Journal of Stroke and Cerebrovascular Diseases*, 21(8), pp. 839-43.

Chen, Y., Bogosavljevic, V., Leys, D., Jovanovic, D., Beslac-Bumbasirevic, L. and Lucas, C. (2011) 'Intravenous thrombolytic therapy in patients with stroke mimics: baseline characteristics and safety profile', *European Journal of Neurology*, 18(10), pp. 1246-50.

Chernyshev, O.Y., Martin-Schild, S., Albright, K., Barreto, A., Misra, V., Acosta, I., Grotta, J. and Savitz, S. (2010) 'Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia', *Neurology*, 74(17), pp. 1340-5.

Choi, B., Tsai, D., McGillivray, C.G., Amedee, C., Sarafin, J.A. and Silver, B. (2014) 'Hospital-directed feedback to Emergency Medical Services improves prehospital performance', *Stroke*, 45(7), pp. 2137-40.

Churilov, L., Fridriksdottir, A., Keshtkaran, M., Mosley, I., Flitman, A. and Dewey, H.M. (2013) 'Decision support in pre-hospital stroke care operations: a case of using simulation to improve eligibility of acute stroke patients for thrombolysis treatment', *Computer & Operations Research*, 40, pp. 2208-2218.

Clarey, J., Lasserson, D., Levi, C., Parsons, M., Dewey, H., Barber, P.A., Quain, D., McElduff, P., Sales, M. and Magin, P. (2014) 'Absolute cardiovascular risk and GP decision making in TIA and minor stroke', *Family Practice*, 31(6), pp. 664-9.

Clark, S., Porter, A., Halter, M., Damiani, M., Dorning, H. and McTigue, M. (2016) 'Data linkage across ambulance services and acute trusts: Assessing the potential for improving patient care', *Emergency Medicine Journal*, 33(9), pp. e12-e12.

Clinical Audit and Research Unit, L.A.S. (2017) *Stroke Annual Report 2016/17*. London Ambulance Service NHS Trust. [Online]. Available at: https://www.londonambulance.nhs.uk/about-us/our-publications/.

College of Paramedics (2016) *Latest news: College membership reaches 10,000 members*. Available at: https://www.collegeofparamedics.co.uk/news/college-membership-reaches-10000-members (Accessed: 29/06/2016).

Collins, G.S., Reitsma, J.B., Altman, D.G. and Moons, K.G.M. (2015) 'Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement', *BMJ*, 350, p. g7594.

Comstedt, P., Storgaard, M. and Lassen, A.T. (2009) 'The Systemic Inflammatory Response Syndrome (SIRS) in acutely hospitalised medical patients: a cohort study', *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 17, pp. 67-67.

Connected Health Cities (2018) *News: Mobile app reduces decision making to 10 seconds for all suspected stroke patients in Greater Manchester*. Available at: https://www.connectedhealthcities.org/2018/04/mobile-app-reduces-decision-making-to-10-seconds-for-all-suspected-stroke-patients-in-greater-manchester/ (Accessed: 06/08/2018).

Cook, C.E. (2008) 'Potential pitfalls of clinical prediction rules', *The Journal of Manual & Manipulative Therapy*, 16(2), pp. 69-71.

Cooper, S. and Endacott, R. (2007) 'Generic qualitative research: a design for qualitative research in emergency care?', *Emergency Medicine Journal*, 24(12), pp. 816-819.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I. and Petticrew, M. (2008) 'Developing and evaluating complex interventions: the new Medical Research Council guidance', *BMJ*, 337.

Crocco, T.J., Kothari, R.U., Sayre, M.R. and Liu, T. (2009) 'A nationwide prehospital stroke survey', *Prehospital Emergency Care*, 3(3), pp. 201-206.

Dami, F., Emery, A., Pasquier, M., Carron, P.N., Fuchs, V., Yersin, B. and Hugli, O. (2017) 'Proposition and operational characteristics of a new dispatch scale to specifically identify acute strokes', *European Journal of Emergency Medicine*, 24(3), pp. 202-207.

Dassan, P., Keir, G., Jager, H. and Brown, M. (2012) 'Value of measuring serum vascular endothelial growth factor levels in diagnosing acute ischemic stroke', *International Journal of Stroke*, 7(6), pp. 454-9.

Dawson, A., Cloud, G., Pereira, A. and Moynihan, B. (2016) 'Stroke mimic diagnoses presenting to a hyperacute stroke unit', *Clinical Medicine*, 16(5), pp. 423-426.

Delva, M., Lytvynenko, N.V. and Delva, I. (2015) 'Conditions that mimic ischemic stroke at hospital admission', *European Journal of Neurology*, 22, p. 800.

Denny, L., Kuhn, L., Risi, L., Richart, R.M., Pollack, A., Lorincz, A., Kostecki, F. and Wright, T.C., Jr. (2000) 'Two-stage cervical cancer screening: an alternative for resource-poor settings', *American Journal of Obstetrics and Gynecology*, 183(2), pp. 383-8.

Devenney, E., Neale, H. and Forbes, R.B. (2014) 'A systematic review of causes of sudden and severe headache (Thunderclap Headache): should lists be evidence based?', *The Journal of Headache and Pain*, 15(1), pp. 49-49.

Doggen, C.J.M., Zwerink, M., Droste, H.M., Brouwers, P.J.A.M., van Houwelingen, G.K., van Eenennaam, F.L. and Egberink, R.E. (2016) 'Prehospital paths and hospital arrival time of patients with acute coronary syndrome or stroke, a prospective observational study', *BMC Emergency Medicine*, 16, p. 3.

Doubilet, P.M. and Cain, K.C. (1985) 'The superiority of sequential over simultaneous testing', *Medical Decision Making*, 5(4), pp. 447-451.

Downing, A., Wilson, R. and Cooke, M. (2005) 'Linkage of ambulance service and accident and emergency department data: a study of assault patients in the west midlands region of the UK', *Injury*, 36(6), pp. 738-744.

Duncan, E., Best, C., Dougall, N., Skar, S., Fitzpatrick, D., Evans, J., Corfield, A., Goldie, I., Maxwell, M., Snooks, H., Stark, C., White, C. and Wojcik, W. (2017) 'Investigating the population characteristics, processes and outcomes of pre-hospital psychiatric and self-harm emergencies in scotland: a national record linkage study', *BMJ Open*, 7(Suppl 3), pp. A11-A12.

Eichel, R., Hur, T., Gomori, J., Cohen, J. and Leker, R. (2013) 'Use of DWI-only MR protocol for screening stroke mimics', *Journal of the Neurological Sciences*, 328(1-2), pp. 37-40.

El Husseini, N. and Goldstein, L. (2013) '"Code stroke": hospitalized versus emergency department patients', *Journal of Stroke and Cerebrovascular Diseases*, 22(4), pp. 345-8.

Emberson, J., Lees, K.R., Lyden, P., Blackwell, L., Albers, G., Bluhmki, E., Brott, T., Cohen, G., Davis, S., Donnan, G., Grotta, J., Howard, G., Kaste, M., Koga, M., von Kummer, R., Lansberg, M., Lindley, R.I., Murray, G., Olivot, J.M., Parsons, M., Tilley, B., Toni, D., Toyoda, K., Wahlgren, N., Wardlaw, J., Whiteley, W., del Zoppo, G.J., Baigent, C., Sandercock, P. and Hacke, W. (2014) '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*, 384(9958), pp. 1929-1935.

Evans, A., Snook, H., Wells, B., Thomas, M., Peconi, J., Turner, J. and Woollard, M. (2009) 'What are the highest priorities for research in prehospital care? Results of a review and consultation exercise', *Emergency Medicine Journal*, 26(10), pp. 1-1.

Evans, M.R.B., White, P., Cowley, P. and Werring, D.J. (2017) 'Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy', *Practical Neurology*, 17(4), pp. 252-265.

Fassbender, K., Balucani, C., Walter, S., Levine, S.R., Haass, A. and Grotta, J. (2013) 'Streamlining of prehospital stroke management: the golden hour', *The Lancet Neurology*, 12(6), pp. 585-596.

Fassbender, K., Grotta, J., Walter, S., Grunwald, I., Ragoschke-Schumm, A. and Saver, J. (2017) 'Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges', *The Lancet Neurology*, 16(3), pp. 227-237.

Feigin, V.L., Lawes, C.M.M., Bennett, D.A., Barker-Collo, S.L. and Parag, V. (2009) 'Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review', *The Lancet Neurology*, 8, pp. 355-69.

Ferro, J.M., Pinto, A.N., Falcao, I., Rodrigues, G., Ferreira, J., Falcao, F., Azevedo, E., Canhao, P., Melo, T. and Rosas, M. (1998) 'Diagnosis of stroke by the nonneurologist a validation study', *Stroke*, 29(6), pp. 1106-1109.

Field, A.P. (2013) *Discovering statistics using IBM SPSS statistics : and sex and drugs and rock 'n' roll*. 4th edn. London: SAGE.

Flynn, D., Nesbitt, D.J., Ford, G.A., McMeekin, P., Rodgers, H., Price, C., Kray, C. and Thomson, R.G. (2015) 'Development of a computerised decision aid for thrombolysis in acute stroke care', *BMC Medical Informatics and Decision Making*, 15, p. 6.

Foerch, C., Niessner, M., Back, T., Bauerle, M., De Marchis, G., Ferbert, A., Grehl, H., Hamann, G., Jacobs, A., Kastrup, A., Klimpe, S., Palm, F., Thomalla, G., Worthmann, H., Sitzer, M. and Group, B.F.S. (2012) 'Diagnostic accuracy of plasma glial fibrillary acidic protein for differentiating intracerebral hemorrhage and cerebral ischemia in patients with symptoms of acute stroke', *Clinical Chemistry*, 58(1), pp. 237-45.

Forest Devices (2018) *Alphastroke: Stroke decisions made smarter*. Available at: https://www.forestdevices.com/ (Accessed: 06/08/2018).

Forster, A., Griebe, M., Wolf, M., Szabo, K., Hennerici, M. and Kern, R. (2012) 'How to identify stroke mimics in patients eligible for intravenous thrombolysis?', *Journal of Neurology*, 259(7), pp. 1347-53.

Fothergill, R.T., Williams, J., Edwards, M.J., Russell, I.T. and Gompertz, P. (2013) 'Does use of the recognition of stroke in the emergency room stroke assessment tool enhance stroke recognition by ambulance clinicians?', *Stroke*, 44(11), pp. 3007-12.

Gargalas, S., Weeks, R., Khan-Bourne, N., Shotbolt, P., Simblett, S., Ashraf, L., Doyle, C., Bancroft, V. and David, A.S. (2017) 'Incidence and outcome of functional stroke mimics admitted to a hyperacute stroke unit', *Journal of Neurology, Neurosurgery and Psychiatry*, 88(1), pp. 2-6.

Geisler, F., Ali, S.F., Ebinger, M., Kunz, A., Rozanski, M., Waldschmidt, C., Weber, J.E., Wendt, M., Winter, B., Schwamm, L.H. and Audebert, H.J. (2018) 'Evaluation of a score for the prehospital distinction between cerebrovascular disease and stroke mimic patients', *International Journal of Stroke*.

Gibson, L.M. and Whiteley, W. (2013) 'The differential diagnosis of suspected stroke: a systematic review', *The Journal of the Royal College of Physicians of Edinburgh*, 43(2), pp. 114-8.

Gioia, L.C., Zewude, R.T., Kate, M.P., Liss, K., Rowe, B.H., Buck, B., Jeerakathil, T. and Butcher, K. (2016) 'Prehospital systolic blood pressure is higher in acute stroke compared with stroke mimics', *Neurology*, 86(23), pp. 2146-2153.

Gonzalez-Garcia, S., Gonzalez-Quevedo, A., Pena-Sanchez, M., Menendez-Sainz, C., Fernandez-Carriera, R., Arteche-Prior, M., Pando-Cabrera, A. and Fernandez-Concepcion, O. (2012) 'Serum neuron-specific enolase and S100 calcium binding protein B biomarker levels do not improve diagnosis of acute stroke', *The Journal of the Royal College of Physicians of Edinburgh*, 42(3), pp. 199-204.

Gonzalez, C.A., Valencia, J.A., Mora, A., Gonzalez, F., Velasco, B., Porras, M.A., Salgado, J., Polo, S.M., Hevia-Montiel, N., Cordero, S. and Rubinsky, B. (2013) 'Volumetric electromagnetic phase-shift spectroscopy of brain edema and hematoma', *PLOS ONE*, 8(5), p. e63223.

Goyal, M., Menon, B.K., van Zwam, W.H., Dippel, D.W.J., Mitchell, P.J., Demchuk, A.M., Dávalos, A., Majoie, C.B.L.M., van der Lugt, A., de Miquel, M.A., Donnan, G.A., Roos, Y.B.W.E.M., Bonafe, A., Jahan, R., Diener, H.-C., van den Berg, L.A., Levy, E.I., Berkhemer, O.A., Pereira, V.M., Rempel, J., Millán, M., Davis, S.M., Roy, D., Thornton, J., Román, L.S., Ribó, M., Beumer, D., Stouch, B., Brown, S., Campbell, B.C.V., van Oostenbrugge, R.J., Saver, J.L., Hill, M.D. and Jovin, T.G. (2016a) 'Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials', *The Lancet*, 387(10029), pp. 1723-1731.

Goyal, N., Male, S., Al Wafai, A., Bellamkonda, S. and Zand, R. (2015) 'Cost burden of stroke mimics and transient ischemic attack after intravenous tissue plasminogen activator treatment', *Journal of Stroke and Cerebrovascular Diseases*, 24(4), pp. 828-833.

Goyal, N., Tsivgoulis, G., Male, S., Metter, E.J., Iftikhar, S., Kerro, A., Chang, J.J., Frey, J.L., Triantafyllou, S., Papadimitropoulos, G., Abedi, V., Alexandrov, A.W., Alexandrov, A.V. and Zand, R. (2016b) 'FABS: An intuitive tool for screening of stroke mimics in the emergency department', *Stroke*, 47(9), pp. 2216-20.

Griffiths, P. and Mooney, G. (2011) *The Paramedic's Guide To Research: An Introduction*. London, UK: Open University Press.

Grimes, D.A. and Schulz, K.F. (2005) 'Refining clinical diagnosis with likelihood ratios', *The Lancet*, 365(9469), pp. 1500-1505.

Grobman, W.A. and Stamilio, D.M. (2006) 'Methods of clinical prediction', *American Journal of Obstetrics and Gynecology*, 194(3), pp. 888-894.

Guillan, M., Alonso-Canovas, A., Gonzalez-Valcarcel, J., Garcia Barragan, N., Garcia Caldentey, J., Hernandez-Medrano, I., Defelipe-Mimbrera, A., Sanchez-Gonzalez, V., Terecoasa, E., Alonso de Lecinana, M. and Masjuan, J. (2012) 'Stroke mimics treated with thrombolysis: further evidence on safety and distinctive clinical features', *Cerebrovascular Diseases*, 34(2), pp. 115-20.

Haddaway, N.R., Collins, A.M., Coughlin, D. and Kirk, S. (2015) 'The role of Google Scholar in evidence reviews and its applicability to grey literature searching', *PLOS ONE*, 10(9), p. e0138237.

Hajian-Tilaki, K. (2013) 'Receiver Operating Characteristic (ROC) curve analysis for medical diagnostic test evaluation', *Caspian Journal of Internal Medicine*, 4(2), pp. 627-635.

Hammermeister, K., Vis, C., Ernst, M., Krivochenitser, R., Oostema, A. and Jones, J. (2013) 'Incidence and clinical characteristics of stroke mimics in the era of thrombolytics', *Annals of Emergency Medicine*, 62(4s), p. S128.

Hand, P., Kwan, J., Lindley, R., Dennis, M. and Wardlaw, J. (2006) 'Distinguishing between stroke and mimic at the bedside: the Brain Attack Study', *Stroke*, 37(3), pp. 769-775.

Haran, H., Bhalla, A., Cluckie, G. and Birns, J. (2016) 'Hyperacute stroke unit training for paramedics', *Journal of Paramedic Practice*, 8(10), pp. 494-498.

Harbison, J., Hossain, O., Jenkinson, D., Davis, J., Louw, S. and Ford, G. (2003) 'Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test', *Stroke*, 34(1), pp. 71-76.

Harbison, J., Massey, A., Barnett, L., Hodge, D. and Ford, G.A. (1999) 'Rapid ambulance protocol for acute stroke', *The Lancet*, 353(9168), p. 1935.

Hatano (1976) 'Experience from a multicentre stroke register', *Bulletin of the World Health Organisation*, 54(5), pp. 541-553.

Hatzitolios, A., Savopoulos, C., Ntaios, G., Papadidaskalou, F., Dimitrakoudi, E., Kosmidou, M., Baltatzi, M. and Karamitsos, D. (2008) 'Stroke and conditions that mimic it: a protocol secures a safe early recognition', *Hippokratia*, 12(2), pp. 98-102.

Haukoos, J.S. and Newgard, C.D. (2007) 'Advanced statistics: Missing data in clinical research—Part 1: An introduction and conceptual framework', *Academic Emergency Medicine*, 14(7), pp. 662-668.

Health and Care Professions Council (2016) *Professions: Paramedics*. Available at: http://www.hcpc-uk.co.uk/aboutregistration/professions/index.asp?id=10 (Accessed: 07/11/2016).

Health Research Authority (2017) *Defining Research*. Available at: http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf (Accessed: 05/08/2018).

Healthcare Cost and Utilization Project (2017) *Clinical Classifications Software (CCS) for ICD-10-CM/PCS*. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/ccs10/ccs10.jsp (Accessed: 04/05/2017).

Hemmen, T., Meyer, B., McClean, T. and Lyden, P. (2008) 'Identification of nonischemic stroke mimics among 411 code strokes at the University of California, San Diego, Stroke Center', *Journal of Stroke and Cerebrovascular Diseases*, 17(1), pp. 23-5.

Hitchcock, K.E. and Holland, C.K. (2010) 'Ultrasound-assisted thrombolysis for stroke therapy: better thrombus break-up with bubbles', *Stroke*, 41(10 Suppl), pp. S50-3.

Hodell, E., Hughes, S.D., Corry, M., Kivlehan, S., Resler, B., Sheon, N. and Govindarajan, P. (2016) 'Paramedic perspectives on barriers to prehospital acute stroke recognition', *Prehospital Emergency Care*, 20(3), pp. 415-424.

Holodinsky, J.K., Patel, A.B., Thornton, J., Kamal, N., Jewett, L.R., Kelly, P.J., Murphy, S., Collins, R., Walsh, T., Cronin, S., Power, S., Brennan, P., O'hare, A., McCabe, D.J.H., Moynihan, B., Looby, S., Wyse, G., McCormack, J., Marsden, P., Harbison, J., Hill, M.D. and Williams, D. (2018) 'Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making', *European Stroke Journal*, 3(2), pp. 126-135.

Holscher, T., Schlachetzki, F., Zimmermann, M., Jakob, W., Ittner, K.P., Haslberger, J., Bogdahn, U. and Boy, S. (2008) 'Transcranial ultrasound from diagnosis to early stroke treatment. 1. Feasibility of prehospital cerebrovascular assessment', *Cerebrovascular Diseases*, 26(6), pp. 659-63.

Hoo, Z.H., Candlish, J. and Teare, D. (2017) 'What is an ROC curve?', *Emerg Med J*, 34(6), pp. 357-359.

Hsieh, M.J., Tang, S.C., Chiang, W.C., Tsai, L.K., Jeng, J.S. and Ma, M.H. (2016) 'Effect of prehospital notification on acute stroke care: a multicenter study', *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, 24, p. 57.

Huang, C.W., Saposnik, G., Fang, J., Steven, D.A. and Burneo, J.G. (2014) 'Influence of seizures on stroke outcomes: A large multicenter study', *Neurology*, 82(9), pp. 768-776.

Iedema, R., Ball, C., Daly, B., Young, J., Green, T., Middleton, P.M., Foster-Curry, C., Jones, M., Hoy, S. and Comerford, D. (2012) 'Design and trial of a new ambulance-to-emergency department handover protocol: 'IMIST-AMBO'', *BMJ Quality & Safety*, 21(8), pp. 627-633.

Intercollegiate Stroke Working Party (2016) *National clinical guideline for stroke*. Physicians, R.C.o. [Online]. Available at: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx.

Iwasaki, S., Hayashi, Y., Seki, A., Nagura, M., Hashimoto, Y., Oshima, G. and Hoshino, T. (2003) 'A model of two-stage newborn hearing screening with automated auditory brainstem response', *International Journal of Pediatric Otorhinolaryngology*, 67(10), pp. 1099-1104.

Jacobson, E.U., Bayer, S., Barlow, J. and Dennis, M. (2015) 'The scope for improvement in hyper-acute stroke care in Scotland', *Operations Research for Health Care*, 6, pp. 50-60.

Jiang, H., Chan, C., Leung, Y., Li, Y., Graham, C. and Rainer, T. (2014) 'Evaluation of the Recognition of Stroke in the Emergency Room (ROSIER) scale in Chinese patients in Hong Kong', *PLOS ONE*, 9(10), p. e109762.

John, A., Okolie, C., Porter, A., Moore, C., Thomas, G., Whitfield, R., Oretti, R. and Snooks, H. (2016) 'Non-accidental non-fatal poisonings attended by emergency ambulance crews: an observational study of data sources and epidemiology', *BMJ Open*, 6(8).

Johnston, S.C., Rothwell, P.M., Nguyen-Huynh, M.N., Giles, M.F., Elkins, J.S., Bernstein, A.L. and Sidney, S. (2007) 'Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack', *Lancet*, 369(9558), pp. 283-92.

Kamal, H., Lopez, V. and Sheth, S.A. (2018) 'Machine learning in acute ischemic stroke neuroimaging', *Frontiers in neurology*, 9, pp. 945-945.

Karlinski, M., Gluszkiewicz, M. and Czlonkowska, A. (2015) 'The accuracy of prehospital diagnosis of acute cerebrovascular accidents: An observational study', *Archives of Medical Science*, 11(3), pp. 530-535.

Kidwell, C.S., Starkman, S., Eckstein, M., Weems, K. and Saver, J.L. (2000) 'Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS)', *Stroke*, 31(1), pp. 71-6.

Knauer, C., Knauer, K., Muller, S., Ludolph, A.C., Bengel, D., Muller, H.P. and Huber, R. (2012) 'A biochemical marker panel in MRI-proven hyperacute ischemic stroke-a prospective study', *BMC Neurology*, 12(14), p. 7 [Online]. Available at: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/431/CN-00900431/frame.html: http://www.biomedcentral.com/content/pdf/1471-2377-12-14.pdf DOI: 10.1186/1471-2377-12-14.

Knottnerus, J.A., van Weel, C. and Muris, J.W.M. (2002) 'Evaluation of diagnostic procedures', *BMJ*, 324(7335), pp. 477-480.

Kose, A., Inal, T., Armagan, E., Kiyak, R. and Demir, A. (2013) 'Conditions that mimic stroke in elderly patients admitted to the emergency department', *Journal of Stroke and Cerebrovascular Diseases*, 22(8), pp. e522-7.

Kothari, R., Barsan, W., Brott, T., Broderick, J. and Ashbrock, S. (1995) 'Frequency and accuracy of prehospital diagnosis of acute stroke', *Stroke*, 26(6), pp. 937-41.

Kothari, R.U., Panicioli, A., Liu, T., Brott, T. and Broderick, J. (1999) 'Cincinnati Prehospital Stroke Scale: reproducibility and validity', *Annals of Emergency Medicine*, 33(4), pp. 373-8.

Kuruvilla, A., Bhattacharya, P., Rajamani, K. and Chaturvedi, S. (2011) 'Factors associated with misdiagnosis of acute stroke in young adults', *Journal of Stroke and Cerebrovascular Diseases*, 20(6), pp. 523-527.

Labopin, M. and Iacobelli, S. (2003) *Statistical guidelines for EBMT*. Available at: https://portal.ebmt.org/sites/clint2/clint/Documents/StatGuidelines_oct2003.pdf (Accessed: 05/08/2018).

Lahr, M.M.H., van der Zee, D.-J., Vroomen, P.C.A.J., Luijckx, G.-J. and Buskens, E. (2013) 'Thrombolysis in acute ischemic stroke: A simulation study to improve pre- and in-hospital delays in community hospitals', *PLOS ONE*, 8(11), p. e79049.

Landis, J.R. and Koch, G.G. (1977) 'The measurement of observer agreement for categorical data', *Biometrics*, 33(1), pp. 159-174.

Laskowitz, D., Kasner, S., Saver, J., Remmel, K. and Jauch, E. (2009) 'Clinical usefulness of a biomarker-based diagnostic test for acute stroke the biomarker rapid assessment in ischemic injury (brain) study', *Stroke*, 40(1), pp. 77-85.

Leonardi-Bee, J., Bath, P.M.W., Phillips, S.J. and Sandercock, P.A.G. (2002) 'Blood pressure and clinical outcomes in the International Stroke Trial', *Stroke*, 33(5), pp. 1315-1320.

Lewandowski, C., Mays-Wilson, K., Miller, J., Penstone, P., Miller, D.J., Bakoulas, K. and Mitsias, P. (2015) 'Safety and outcomes in stroke mimics after intravenous tissue plasminogen activator administration: A single-center experience', *Journal of Stroke and Cerebrovascular Diseases*, 24(1), pp. 48-52.

Liao, L. and Mark, D.B. (2003) 'Clinical prediction models: are we building better mousetraps?', *Journal of the American College of Cardiology*, 42(5), pp. 851-853.

Liberman, A.L., Liotta, E.M., Caprio, F.Z., Ruff, I., Maas, M.B., Bernstein, R.A., Khare, R., Bergman, D. and Prabhakaran, S. (2015) 'Do efforts to decrease door-to-needle time risk increasing stroke mimic treatment rates?', *Neurology: Clinical Practice*, 5(3), pp. 247-252.

Libman, R., Wirkowski, E., Alvir, J. and Rao, T. (1995) 'Conditions that mimic stroke in the emergency department. Implications for acute stroke trials', *Archives of Neurology*, 52(11), pp. 1119-22.

Lin, C.B., Peterson, E.D., Smith, E.E., Saver, J.L., Liang, L., Xian, Y., Olson, D.M., Shah, B.R., Hernandez, A.F., Schwamm, L.H. and Fonarow, G.C. (2012) 'Emergency medical service hospital prenotification is associated with improved evaluation and treatment of acute ischemic stroke', *Circulation. Cardiovascular quality and outcomes*, 5(4), pp. 514-22.

Lip, G.H. and Lane, D.A. (2015) 'Stroke prevention in atrial fibrillation: A systematic review', *JAMA*, 313(19), pp. 1950-1962.

Llanes, J.N., Kidwell, C.S., Starkman, S., Leary, M.C., Eckstein, M. and Saver, J.L. (2004) 'The Los Angeles Motor Scale (LAMS): a new measure to characterize stroke severity in the field', *Prehospital Emergency Care*, 8(1), pp. 46-50.

Long, B. and Koyfman, A. (2017) 'Clinical mimics: An emergency medicine-focused review of stroke mimics', *Journal of Emergency Medicine*, 52(2), pp. 176-183.

Loomis, C. and Mullen, M.T. (2014) 'Differentiating facial weakness caused by Bell's Palsy vs. acute stroke; Can you tell the difference?', *Journal of Emergency Medical Services (JEMS)*, 39(5) [Online]. Available at: http://www.jems.com/articles/print/volume-39/issue-5/features/differentiating-facial-weakness-caused-b.html (Accessed: Wed 7th May).

Lorenz, M.W., Lauer, A. and Foerch, C. (2015) 'Quantifying the benefit of prehospital rapid treatment in acute stroke: Benchmark for future innovative clinical trials', *Stroke*, 46(11), pp. 3168-3176.

Luger, S., Witsch, J., Dietz, A., Hamann, G.F., Minnerup, J., Schneider, H., Sitzer, M., Wartenberg, K.E., Niessner, M. and Foerch, C. (2017) 'Glial fibrillary acidic protein serum levels distinguish between intracerebral hemorrhage and cerebral ischemia in the early phase of stroke', *Clinical Chemistry*, 63(1), pp. 377-385.

Lutman, D., Montgomery, M., Ramnarayan, P. and Petros, A. (2008) 'Ambulance and aeromedical accident rates during emergency retrieval in Great Britain', *Emergency Medicine Journal*, 25(5), pp. 301-2.

Ma, H., Parsons, M., Campbell, B., Levi, C., Yan, B., Churilov, L., Hsu, C., Thijs, V., Mitchell, P., Meretoja, A., Davis, S. and Donnan, G. (2018) 'Extending the time for thrombolysis in emergency neurological deficits - EXTEND', *International Journal of Stroke*, 13(2S).

Macaskill, P., Walter, S.D., Irwig, L. and Franco, E.L. (2002) 'Assessing the gain in diagnostic performance when combining two diagnostic tests', *Statistics in Medicine*, 21, pp. 2527-2546.

Mao, H., Lin, P., Mo, J., Li, Y., Chen, X., Rainer, T.H. and Jiang, H. (2016) 'Development of a new stroke scale in an emergency setting', *BMC Neurology*, 16, p. 168.

Martin, P., Young, G., Enevoldson, T. and Humphrey, P. (1997) 'Overdiagnosis of TIA and minor stroke: experience at a regional neurovascular clinic', *QJM : monthly journal of the Association of Physicians*, 90(12), pp. 759-63.

Mason, S., Knowles, E., Colwell, B., Dixon, S., Wardrope, J., Gorringe, R., Snooks, H., Perrin, J. and Nicholl, J. (2007) 'Effectiveness of paramedic practitioners in attending 999 calls from elderly people in the community: cluster randomised controlled trial', *BMJ*, 335(7626), p. 919.

Mattila, O.S., Harve, H., Pihlasviita, S., Ritvonen, J., Sibolt, G., Pystynen, M., Strbian, D., Curtze, S., Kuisma, M., Tatlisumak, T. and Lindsberg, P.J. (2016) 'Ultra-acute diagnostics for stroke: Large-scale implementation of prehospital biomarker sampling', *Acta Neurologica Scandinavica.*

McClelland, G. (2013) 'The research paramedic: a new role', *Journal of Paramedic Practice*, 5(10), pp. 582-586.

McClelland, G., Flynn, D., Rodgers, H. and Price, C. (2017) 'A survey of UK paramedics' views about their stroke training, current practice and the identification of stroke mimics', *British Paramedic Journal*, 2(1), pp. 4-15.

McClelland, G., Flynn, D., Rodgers, H. and Price, C.I. (2015) *A systematic review of the clinical and demographic characteristics of adult patients with stroke mimics*. Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026457 (Accessed: 17/07/2017).

McClelland, G., Rodgers, H., Flynn, D. and Price, C.I. (2018) 'The frequency, characteristics and aetiology of stroke mimic presentations: a narrative review', *Eur J Emerg Med*, [Online]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29727304 DOI: 10.1097/MEJ.0000000000000550 (Accessed: May 1).

McKinney, J.S., Mylavarapu, K., Lane, J., Roberts, V., Ohman-Strickland, P. and Merlin, M.A. (2013) 'Hospital prenotification of stroke patients by emergency medical services improves stroke time targets', *Journal of Stroke & Cerebrovascular Diseases*, 22(2), pp. 113-8.

McManamny, T., Sheen, J., Boyd, L. and Jennings, P.A. (2014) 'Mixed methods and its application in prehospital research', *Journal of Mixed Methods Research*, 9(3), pp. 214-231.

McMeekin, P., Gray, J., Ford, G.A., Rodgers, H. and Price, C.I. (2013) 'Modelling the efficiency of local versus central provision of intravenous thrombolysis after acute ischemic stroke', *Stroke*, 44(11), pp. 3114-9.

McMeekin, P., White, P., James, M.A., Price, C.I., Flynn, D. and Ford, G.A. (2017) 'Estimating the number of UK stroke patients eligible for endovascular thrombectomy', *European Stroke Journal*, 2(4), pp. 319-326.

Medfield Diagnostics (2018) *Products: Strokefinder*. Available at: http://www.medfielddiagnostics.com/en/products/ (Accessed: 06/08/2018).

Mehta, S., Vora, N., Edgell, R.C., Allam, H., Alawi, A., Koehne, J., Kumar, A., Feen, E., Cruz-Flores, S. and Alshekhlee, A. (2014) 'Stroke mimics under the drip-and-ship paradigm', *Journal of Stroke & Cerebrovascular Diseases*, 23(5), pp. 844-849.

Merino, J., Luby, M., Benson, R., Davis, L., Hsia, A., Latour, L., Lynch, J. and Warach, S. (2013) 'Predictors of acute stroke mimics in 8187 patients referred to a stroke service', *Journal of Stroke & Cerebrovascular Diseases*, 22(8), pp. e397-403.

Milne, M.S., Holodinsky, J.K., Hill, M.D., Nygren, A., Qiu, C., Goyal, M. and Kamal, N. (2017) 'Drip 'n ship versus mothership for endovascular treatment: Modeling the best transportation options for optimal outcomes', *Stroke*, 48(3), pp. 791-794.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. and Group, P. (2009) 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', *BMJ*, 339, p. b2535.

Monks, T., Pearn, K. and Allen, M. (2015) 'Simulation of stroke care systems', *Proceedings of the 2015 Winter Simulation Conference*. Huntington Beach, California. IEEE Press.

Monks, T., Pitt, M., Stein, K. and James, M. (2012) 'Maximizing the population benefit from thrombolysis in acute ischemic stroke: A modeling study of in-hospital delays', *Stroke*, 443(10), pp. 2706-2711.

Monks, T., Worthington, D., Allen, M., Pitt, M., Stein, K. and James, M.A. (2016) 'A modelling tool for capacity planning in acute and community stroke services', *BMC Health Services Research*, 16(1), p. 530.

Montaner, J., Mendioroz, M., Ribo, M., Delgado, P., Quintana, M., Penalba, A., Chacon, P., Molina, C., Fernandez-Cadenas, I., Rosell, A. and Alvarez-Sabin, J. (2011) 'A panel of biomarkers including caspase-3 and D-dimer may differentiate acute stroke from stroke-mimicking conditions in the emergency department', *Journal of Internal Medicine*, 270(2), pp. 166-74.

Moons, K.G.M., Altman, D.G., Vergouwe, Y. and Royston, P. (2009a) 'Prognosis and prognostic research: application and impact of prognostic models in clinical practice', *BMJ*, 338, p. b606.

Moons, K.G.M., Royston, P., Vergouwe, Y., Grobbee, D.E. and Altman, D.G. (2009b) 'Prognosis and prognostic research: what, why, and how?', *BMJ*, 338, p. b375.

Morris, S., Hunter, R.M., Ramsay, A.I.G., Boaden, R., McKevitt, C., Perry, C., Pursani, N., Rudd, A.G., Schwamm, L.H., Turner, S.J., Tyrrell, P.J., Wolfe, C.D.A. and Fulop, N.J. (2014) 'Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis', *BMJ*, 349.

Mosley, I., Nicol, M., Donnan, G., Patrick, I., Kerr, F. and Dewey, H. (2007) 'The impact of ambulance practice on acute stroke care', *Stroke*, 38(10), pp. 2765-70.

Mukaka, M.M. (2012) 'A guide to appropriate use of correlation coefficient in medical research', *Malawi Medical Journal*, 24(3), pp. 69-71.

Mumma, B.E., Diercks, D.B., Danielsen, B. and Holmes, J.F. (2015) 'Probabilistic linkage of prehospital and outcomes data in out-of-hospital cardiac arrest', *Prehospital Emergency Care*, 19(3), pp. 358-364.

Munro, S.F.S., Cooke, D., Kiln-Barfoot, V. and Quinn, T. (2018) 'The use and impact of 12-lead electrocardiograms in acute stroke patients: A systematic review', *European Heart Journal: Acute Cardiovascular Care*, 7(3), pp. 257-263.

Musuka, T.D., Wilton, S.B., Traboulsi, M. and Hill, M.D. (2015) 'Diagnosis and management of acute ischemic stroke: Speed is critical', *Canadian Medical Association Journal*, 187(12), pp. 887-893.

Nacu, A., Fromm, A., Sand, K.M., Waje-Andreassen, U., Thomassen, L. and Naess, H. (2016) 'Age dependency of ischaemic stroke subtypes and vascular risk factors in western Norway: the Bergen Norwegian Stroke Cooperation Study', *Acta Neurologica Scandinavica*, 133(3), pp. 202-207.

National Ambulance Service Medical Directors, N. (2014) *Future national clinical priorities for ambulance services in England*. [Online]. Available at: https://aace.org.uk/wp-content/uploads/2014/05/Future-national-clinical-priorities-for-ambulance-services-in-England-FINAL-2.pdf.

National Institute for Health and Care Excellence, N. (2017) *Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. Clinical guideline (CG68): Introduction*. Available at: https://www.nice.org.uk/guidance/cg68/chapter/Introduction (Accessed: 05/08/2018).

Natteru, P., Mohebbi, M.R., George, P., Wisco, D., Gebel, J. and Newey, C.R. (2016) 'Variables that best differentiate in-patient acute stroke from stroke-mimics with acute neurological deficits', *Stroke Research and Treatment*, 2016(4393127) [Online]. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed18b&AN=613974720.

Newton, M., Tunn, E., Moses, I., Ratcliffe, D. and Mackway-Jones, K. (2014) 'Clinical navigation for beginners: the clinical utility and safety of the Paramedic Pathfinder', *Emergency Medicine Journal*, 31(e1), pp. e29-34.

NHS England (2017) *News: Stroke patients in England set to receive revolutionary new treatment*. Available at: https://www.england.nhs.uk/2017/04/stroke-patients-in-england-set-to-receive-revolutionary-new-treatment/ (Accessed: 11/04/2017).

NIHR Dissemination Centre (2016) *Care at the scene: Research for ambulance services*. [Online]. Available at: https://www.dc.nihr.ac.uk/themed-reviews/Care%20at%20the%20scene%20final%20for%20web.pdf.

Nogueira, R.G., Jadhav, A.P., Haussen, D.C., Bonafe, A., Budzik, R.F., Bhuva, P., Yavagal, D.R., Ribo, M., Cognard, C., Hanel, R.A., Sila, C.A., Hassan, A.E., Millan, M., Levy, E.I., Mitchell, P., Chen, M., English, J.D., Shah, Q.A., Silver, F.L., Pereira, V.M., Mehta, B.P., Baxter, B.W., Abraham, M.G., Cardona, P., Veznedaroglu, E., Hellinger, F.R., Feng, L., Kirmani, J.F., Lopes, D.K., Jankowitz, B.T., Frankel, M.R., Costalat, V., Vora, N.A., Yoo, A.J., Malik, A.M., Furlan, A.J., Rubiera, M., Aghaebrahim, A., Olivot, J.-M., Tekle, W.G., Shields, R., Graves, T., Lewis, R.J., Smith, W.S., Liebeskind, D.S., Saver, J.L. and Jovin, T.G. (2018) 'Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct', *New England Journal of Medicine*, 378(1), pp. 11-21.

Nor, A.M., Davis, J., Sen, B., Shipsey, D., Louw, S.J., Dyker, A.G., Davis, M. and Ford, G.A. (2005) 'The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument', *The Lancet Neurology*, 4(11), pp. 727-34.

Nor, A.M., McAllister, C., Louw, S.J., Dyker, A.G., Davis, M., Jenkinson, D. and Ford, G.A. (2004) 'Agreement between ambulance paramedic-and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients', *Stroke*, 35(6), pp. 1355-1359.

Norris, J.W. and Hachinski, V.C. (1982) 'Misdiagnosis of stroke', *The Lancet*, 319(8267), pp. 328-331.

North East Ambulance Service NHS Foundation Trust (2018) *North East Ambulance Service: Who we are and what we do*. Available at: https://www.neas.nhs.uk/about-us/who-we-are-and-what-we-do.aspx (Accessed: 06/08/2018).

O'Brien, P., Ryder, D. and Twomey, C. (1987) 'The role of computed tomography brain scan in the diagnosis of acute stroke in the elderly', *Age & Ageing*, 16(5), pp. 319-322.

O'Connell, G.C., Petrone, A.B., Treadway, M.B., Tennant, C.S., Lucke-Wold, N., Chantler, P.D. and Barr, T.L. (2016) 'Machine-learning approach identifies a pattern of gene expression in peripheral blood that can accurately detect ischaemic stroke', *NPJ Genomic Medicine*, 1, p. 16038 [Online] DOI: http://dx.doi.org/10.1038/npjgenmed.2016.38.

Oostema, J.A., Nasiri, M., Chassee, T. and Reeves, M.J. (2014) 'The quality of prehospital ischemic stroke care: compliance with guidelines and impact on in-hospital stroke response', *Journal of Stroke & Cerebrovascular Diseases*, 23(10), pp. 2773-9.

Oostema, J.A., Tecos, M., Sleight, D. and Mavis, B. (2016) 'Paramedic perspectives on prehospital stroke care: A qualitative analysis', *Stroke*, 47(Suppl 1), p. AWP247.

Pearson, C., Przyklenk, K., Mika, V.H., Ayaz, S.I., Ellis, M., Varade, P., Tolomello, R. and Welch, R.D. (2017) 'Utility of point of care assessment of platelet reactivity (using the PFA-100) to aid in diagnosis of stroke', *American Journal of Emergency Medicine.*, 35(5), p. 802.

Penaloza-Ramos, M.C., Sheppard, J.P., Jowett, S., Barton, P., Mant, J., Quinn, T., Mellor, R.M., Sims, D., Sandler, D., McManus, R.J. and Investigators., o.b.o.t.B.a.B.C.C.f.L.i.A.H.R.a.C. (2014) 'Cost-effectiveness of optimizing acute stroke care services for thrombolysis', *Stroke*, 45(2), pp. 553-562.

Penn, A., Balshaw, R., Lesperance, M., Saly, V., Jackson, A., Smith, D., Votova, K., Lu, L., Morrison, J., Coutts, S. and Borchers, C. (2016) 'Exploring protein quantitation methods to detect useful plasma biomarkers for distinguishing ischemic stroke from mimic', *Neurology*, 86(16 Suppl 1).

Perez de la Ossa, N., Carrera, D., Gorchs, M., Querol, M., Millan, M., Gomis, M., Dorado, L., Lopez-Cancio, E., Hernandez-Perez, M., Chicharro, V., Escalada, X., Jimenez, X. and Davalos, A. (2014) 'Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale', *Stroke*, 45(1), pp. 87-91.

Perez de la Ossa, N., Ribo, M., Jimenez, X. and Abilleira, S. (2016) 'Prehospital scales to identify patients with large vessel occlusion: It is time for action', *Stroke*, 47(11), pp. 2877-2878.

Perkins, G.D., Lall, R., Quinn, T., Deakin, C.D., Cooke, M.W., Horton, J., Lamb, S.E., Slowther, A., Woollard, M., Carson, A., Smyth, M., Whitfield, R., Williams, A., Pocock, H., Black, J.J.M., Wright, J., Han, K. and Gates, S. (2015) 'Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial', *The Lancet*, 385(9972), pp. 947-955.

Petrie, A. and Sabin, C. (2009) *Medical Statistics at a Glance*. Third edn. UK: Wiley-Blackwell.

Pitt, M., Monks, T., Crowe, S. and Vasilakis, C. (2016) 'Systems modelling and simulation in health service design, delivery and decision making', *BMJ Quality & Safety*, 25(1), pp. 38-45.

Pollard, J. and Black, S. (2015) 'Do paramedics find it beneficial to learn the diagnosis given to their patients in the emergency department?', *Emergency Medicine Journal*, 32(5), pp. 421-421.

Pope, C. and Mays, N. (2006) *Qualitative research in health care*. Oxford, UK: Blackwell Publishing Ltd.

Porter, A., Dale, J., Foster, T., Logan, P., Wells, B. and Snooks, H. (2018) 'Implementation and use of computerised clinical decision support (CCDS) in emergency pre-hospital care: a qualitative study of paramedic views and experience using Strong Structuration Theory', *Implementation Science*, 13(1), p. 91.

Public Health England (2013) *NHS population screening explained*. Available at: https://www.gov.uk/guidance/nhs-population-screening-explained (Accessed: 05/08/2018).

Puolakka, T., Strbian, D., Harve, H., Kuisma, M. and Lindsberg, P., J. (2016) 'Prehospital phase of the stroke chain of survival: A prospective observational study', *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, 5(5), p. e002808.

Purrucker, J.C., Härtig, F., Richter, H., Engelbrecht, A., Hartmann, J., Auer, J., Hametner, C., Popp, E., Ringleb, P.A., Nagel, S. and Poli, S. (2017) 'Design and validation of a clinical scale for prehospital stroke recognition, severity grading and prediction of large vessel occlusion: the shortened NIH Stroke Scale for emergency medical services', *BMJ Open*, 7(9), p. e016893.

Putaala, J. (2016) 'Ischemic stroke in the young: Current perspectives on incidence, risk factors, and cardiovascular prognosis', *European Stroke Journal*, 1(1), pp. 28-40.

Quenardelle, V., Lauer-Ober, V., Zinchenko, I., Bataillard, M., Rouyer, O., Beaujeux, R., Pop, R., Meyer, N., Delplancq, H., Kremer, S., Marescaux, C., Geny, B. and Wolff, V. (2016) 'Stroke mimics in a stroke care pathway based on MRI screening', *Cerebrovascular Diseases*, 42(3-4), pp. 205-212.

Ramadan, H., Patterson, C., Maguire, S., Melvin, I., Adamson, J., Kain, K., Teale, E. and Forster, A. (2015) '12-month data on frequency and pattern of stroke mimic diagnosis in a district general hospital in the UK', *International Journal of Stroke*, 10, p. 121.

Ramsay, A.I., Morris, S., Hoffman, A., Hunter, R.M., Boaden, R., McKevitt, C., Perry, C., Pursani, N., Rudd, A.G., Turner, S.J., Tyrrell, P.J., Wolfe, C.D. and Fulop, N.J. (2015) 'Effects of centralizing acute stroke services on stroke care provision in two large metropolitan areas in England', *Stroke*, 46(8), pp. 2244-51.

RCP, R.C.o.P. (2012) *National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS*. London: Physicians, R.C.o.

RCP, R.C.o.P. (2015) *Sentinel Stroke National Audit Programme (SSNAP): Clinical audit July - September 2014 public report: National results*. [Online]. Available at: https://www.strokeaudit.org/Documents/National/Clinical/JulSep2014/JulSep2014-PublicReport.aspx.

RCP, R.C.o.P. (2016) *Mind the gap: the third SSNAP annual report* [Online]. Available at: https://www.strokeaudit.org/Documents/AnnualReport/2015-16-SSNAP-Annual-Report.aspx.

RCP, R.C.o.P. (2017a) *Sentinel Stroke National Audit Programme (SSNAP): Clinical audit: December 2016 – March 2017: Public Report: National results*. [Online]. Available at: https://www.strokeaudit.org/Documents/National/Clinical/DecMar2017/DecMar2017-PublicReport.aspx.

RCP, R.C.o.P. (2017b) *SSNAP, Results, Clinical Audit, Regional*. Available at: https://www.strokeaudit.org/results/Clinical-audit/Regional-Results.aspx (Accessed: 05/08/2018).

RCP, R.C.o.P. (2017c) *SSNAP: Health Economics*. Available at: https://www.strokeaudit.org/Health-Economics.aspx (Accessed: 06/08/2018).

Rees, N., Hampton, C., Bulger, J., Ali, K., Quinn, T., Ford, G., Akbari, A., Ward, M., Porter, A., Jones, C. and Snooks, H. (2018) 'TIA prehospital referral feasibility trial (TIER): recruitment and intervention usage', *BMJ Open*, 8(Suppl 1), pp. A28-A28.

Reid, J.M., Currie, Y. and Baird, T. (2012) 'Non-stroke admissions to a hyperacute stroke unit', *Scottish Medical Journal*, 57(4), pp. 209-11.

Restrepo, L., Sanossian, N., Liebeskind, D., Ali, L., Starkman, S. and Saver, J. (2010) 'Stroke mimics in a prehospital stroke treatment trial', *Stroke*, 41(4), p. e201 [Online]. Available at: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/091/CN-00758091/frame.html.

Restrepo, L., Sheth, S.A., Stafford, P., Saver, J. and Johnston, S.A. (2016) 'A blood test capable of discriminating between real strokes and mimics', *Stroke*, 47(Suppl 1), p. AWP218.

Richoz, B., Hugli, O., Dami, F., Carron, P.N., Faouzi, M. and Michel, P. (2015) 'Acute stroke chameleons in a university hospital: Risk factors, circumstances, and outcomes', *Neurology*, 85(6), pp. 505-11.

Roberts-Andreou, L. (2016) *Freedom of information request to West Midlands Ambulance Service NHS Foundation Trust*. Available at: https://www.whatdotheyknow.com/request/stroke_pathways (Accessed: 05/08/2018).

Rostanski, S., Williams, O., Stillman, J., Boehme, A., Marshall, R. and Willey, J. (2016) 'Stroke mimic treatment rates and physician-patient language discordance', *Stroke*, 47, p. AWMP80.

Royston, P., Moons, K.G.M., Altman, D.G. and Vergouwe, Y. (2009) 'Prognosis and prognostic research: Developing a prognostic model', *BMJ*, 338, p. b604.

Rudd, M., Buck, D., Ford, G.A. and Price, C.I. (2016a) 'A systematic review of stroke recognition instruments in hospital and prehospital settings', *Emergency Medicine Journal*, 33(11), pp. 818-822.

Rudd, M.P., Martin, A.J., Harrison, A. and Price, C.I. (2016b) 'Agreement between ambulance and hospital records for information promoting urgent stroke treatment decisions', *European Journal of Emergency Medicine*, 23(1), pp. 24-27.

Sacco, R.L. (1997) 'Risk factors, outcomes, and stroke subtypes for ischemic stroke', *Neurology*, 49(5 Suppl 4), pp. S39-S44.

Sanddal, N.D., Sanddal, T.L. and Mann, C.N. (2017) 'The impact of challenges in data linkage between prehospital and hospital trauma registries', *Annals of Trauma and Acute Care*, 1(1), pp. 1-2.

Sanddal, T.L., Sanddal, N.D., Ward, N. and Stanley, L. (2010) 'Ambulance crash characteristics in the US defined by the popular press: A retrospective analysis', *Emergency Medicine International*, 2010, p. 525979.

Sarikaya, H., Yilmaz, M.B., Luft, A. and Gantenbein, A. (2012) 'Different pattern of clinical deficits in stroke mimics treated with intravenous thrombolysis', *European Neurology*, 68(6), pp. 344-9.

Satya-Murti, S. and Lockhart, J. (2015) 'Recognizing and reducing cognitive bias in clinical and forensic neurology', *Neurology: Clinical Practice*, 5(5), pp. 389-396.

Saver, J.L., Starkman, S., Eckstein, M., Stratton, S.J., Pratt, F.D., Hamilton, S., Conwit, R., Liebeskind, D.S., Sung, G., Kramer, I., Moreau, G., Goldweber, R. and Sanossian, N. (2015) 'Prehospital use of magnesium sulfate as neuroprotection in acute stroke', *The New England Journal of Medicine*, 372(6), pp. 528-36 [Online]. Available at: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/727/CN-01047727/frame.html DOI: 10.1056/NEJMoa1408827.

Scott, P. and Silbergleit, R. (2003) 'Misdiagnosis of stroke in tissue plasminogen activator-treated patients: characteristics and outcomes', *Annals of Emergency Medicine*, 42(5), pp. 611-8.

Sequeira, D., Martin-Gill, C., Kesinger, M.R., Thompson, L.R., Jovin, T.G., Massaro, L.M. and Guyette, F.X. (2016) 'Characterizing strokes and stroke mimics transported by helicopter emergency medical services', *Prehospital Emergency Care*, 20(6), pp. 723-728.

Seymour, C.W., Rea, T.D., Kahn, J.M., Walkey, A.J., Yealy, D.M. and Angus, D.C. (2012) 'Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome', *American Journal of Respiratory and Critical Care Medicine*, 186(12), pp. 1264-71.

Sharma, R., Macy, S., Richardson, K., Lokhnygina, Y. and Laskowitz, D.T. (2014) 'A blood-based biomarker panel to detect acute stroke', *Journal of Stroke & Cerebrovascular Diseases*, 23(5), pp. 910-918.

Sharobeem, K.M., Awad, F. and Wilkinson, J. (2016) 'A diagnostic challenge: A stroke or a mimic? A prospective observational study of patients presenting with suspected acute stroke in a UK hospital', *European Stroke Journal*, 1(1S), p. 436.

Shaw, L., Ford, G.A., Exley, C., Flynn, D., McMeekin, P., Rodgers, H., Snooks, H., Tyrell, P., Vale, L. and Price, C. (2016) 'Paramedic Acute Stroke Treatment Assessment (PASTA) trial', *Emergency Medicine Journal*, 33(9), pp. e10-e10.

Sheppard, J.P., Mellor, R.M., Greenfield, S., Mant, J., Quinn, T., Sandler, D., Sims, D., Singh, S., Ward, M. and McManus, R.J. (2015a) 'The association between prehospital care and in-hospital treatment decisions in acute stroke: a cohort study', *Emergency Medicine Journal*, 32(2), pp. 93-99.

Sheppard, J.P., Mellor, R.M., Greenfield, S., Mant, J., Quinn, T., Sandler, D., Sims, D., Singh, S., Ward, M., McManus, R.J. and investigators, C.B. (2015b) 'The association between prehospital care and in-hospital treatment decisions in acute stroke: a cohort study', *Emergency Medicine Journal*, 32(2), pp. 93-9.

Shribman, S.E., Khan, A., Williamson, J., Vaid, N., Ip, D. and Gompertz, P. (2013) 'Stroke-mimics: The experience at an east London hyper-acute stroke unit centre', *Cerebrovascular Diseases*, 35(Suppl 3), p. 687.

Shukla, G.J. and Zimetbaum, P.J. (2006) 'Syncope', *Circulation*, 113(16), pp. e715-e717.

Siddiqui, F., Khan, N., Goehl, C., Endris, L. and Elias, A. (2016) 'Developing a novel algortihm to help identify acute stroke mimics', *European Stroke Journal*, 1(1S).

Siddiqui, M., Soliman, M., Booth, S., Callum, A., Boyle, K., Khadjooi, K., O'Brien, E., Martin, P. and Warburton, E. (2013) 'Ambulance triage of stroke in semi-rural England results in high mimic transfer rates', *International Journal of Stroke*, 8(Suppl 3), p. 1.

Silvestrelli, G., Parnetti, L., Paciaroni, M., Caso, V., Corea, F., Vitali, R., Capocchi, G. and Agnelli, G. (2006) 'Early admission to stroke unit influences clinical outcome', *European Journal of Neurology*, 13(3), pp. 250-5.

Siriwardena, A.N., Shaw, D., Essam, N., Togher, F.J., Davy, Z., Spaight, A. and Dewey, M. (2014) 'The effect of a national quality improvement collaborative on prehospital care for acute myocardial infarction and stroke in England', *Implementation Science*, 9, pp. 17-17.

Sirriyeh, R., Lawton, R., Gardner, P. and Armitage, G. (2012) 'Reviewing studies with diverse designs: the development and evaluation of a new tool', *Journal of Evaluation in Clinical Practice*, 18(4), pp. 746-52.

Sivakumaran, P., Gill, D., Mahir, G., Baheerathan, A. and Kar, A. (2016) 'A retrospective cohort study on the use of intravenous thrombolysis in stroke mimics', *Journal of Stroke and Cerebrovascular Diseases*, 25(5), pp. 1057-1061.

Snow, S.J. (2013) 'Translating new knowledge into practices: reconceptualising stroke as an emergency condition', *Chronic Illness*, 9(3), pp. 191-201.

Southend University Hospital (2018) *Southend University Hospital plans Mobile Stroke Unit project*. Available at: http://www.southend.nhs.uk/about-us/media-centre/southend-news/nr18-(2018)/ (Accessed: 06/08/2018).

Staubach, S., Soekeland, K., Ledwoch, J., Segerer, M., Strohm, H. and Mudra, H. (2016) 'Stroke rates after carotid artery stenting depend on study-specific definitions', *EuroIntervention*, 12(4), pp. 526-30.

Steyerberg, E.W., Moons, K.G.M., van der Windt, D.A., Hayden, J.A., Perel, P., Schroter, S., Riley, R.D., Hemingway, H., Altman, D.G. and for the, P.G. (2013) 'Prognosis research strategy (PROGRESS) 3: Prognostic model research', *PLOS Medicine*, 10(2), p. e1001381.

Stiell, I. (1996) 'Ottawa ankle rules', *Canadian Family Physician*, 42, pp. 478-80.

Stroke Unit Trialists Collaboration (2013) 'Organised inpatient (stroke unit) care for stroke', *Cochrane Database of Systematic Reviews*, (9), p. CD000197.

Szumilas, M. (2010) 'Explaining odds ratios', *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 19(3), pp. 227-229.

Taguchi, H., Hasegawa, Y., Bandoh, K., Koyasu, H., Watanabe, Y., Yamashita, K., Shimazaki, K., Shima, H., Miyakawa, M. and Niwa, Y. (2016) 'Implementation of a community-based triage for patients with suspected transient ischemic attack or minor stroke study: A prospective multicenter observational study', *Journal of Stroke and Cerebrovascular Diseases*, 25(4), pp. 745-751.

Tentschert, S., Wimmer, R., Greisenegger, S., Lang, W. and Lalouschek, W. (2005) 'Headache at stroke onset in 2196 patients with ischemic stroke or transient ischemic attack', *Stroke*, (36), pp. e1-e3.

The Comptroller and Auditor General (2010) *Progress in improving stroke care*. Office, N.A. [Online]. Available at: www.nao.org.uk/stroke2010.

The Stroke Association (2018) *State of the nation: Stroke statistics February 2018*. [Online]. Available at: https://www.stroke.org.uk/system/files/sotn_2018.pdf.

Thomalla, G., Simonsen, C.Z., Boutitie, F., Andersen, G., Berthezene, Y., Cheng, B., Cheripelli, B., Cho, T.-H., Fazekas, F., Fiehler, J., Ford, I., Galinovic, I., Gellissen, S., Golsari, A., Gregori, J., Günther, M., Guibernau, J., Häusler, K.G., Hennerici, M., Kemmling, A., Marstrand, J., Modrau, B., Neeb, L., Perez de la Ossa, N., Puig, J., Ringleb, P., Roy, P., Scheel, E., Schonewille, W., Serena, J., Sunaert, S., Villringer, K., Wouters, A., Thijs, V., Ebinger, M., Endres, M., Fiebach, J.B., Lemmens, R., Muir, K.W., Nighoghossian, N., Pedraza, S. and Gerloff, C. (2018) 'MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset', *New England Journal of Medicine*, 379(7), pp. 611-622.

Tobin, W.O., Hentz, J.G., Bobrow, B.J. and Demaerschalk, B.M. (2009) 'Identification of stroke mimics in the emergency department setting', *Journal of Brain Disease*, 1, pp. 19-22.

Tsivgoulis, G., Alexandrov, A.V., Chang, J., Sharma, V.K., Hoover, S.L., Lao, A.Y., Liu, W., Stamboulis, E.l., Alexandrov, A.W. and Malkoff, M.D. (2011) 'Safety and outcomes of intravenous thrombolysis in stroke mimics: A 6-year, single-care center study and a pooled analysis of reported series', *Stroke*, 42(6), pp. 1771-1774.

Tsivgoulis, G., Zand, R., Katsanos, A.H., Goyal, N., Uchino, K., Chang, J., Dardiotis, E., Putaala, J., Alexandrov, A.W., Malkoff, M.D. and Alexandrov, A.V. (2015) 'Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis', *Stroke*, 46(5), pp. 1281-7.

Tuntiyatorn, L., Saksornchai, P. and Tunlayadechanont, S. (2013) 'Identification of stroke mimics among clinically diagnosed acute strokes', *Journal of the Medical Association of Thailand*, 96(9), pp. 1191-8.

Turner, M., Barber, M., Dodds, H., Dennis, M., Langhorne, P. and Macleod, M.J. (2015) 'The impact of stroke unit care on outcome in a Scottish stroke population, taking into account case mix and selection bias', *Journal of Neurology, Neurosurgery, and Psychiatry*, 86(3), pp. 314-8.

UEC Review Team and ECIST (2015) *Transforming urgent and emergency care services in England*. NHS England. [Online]. Available at: https://www.nhs.uk/NHSEngland/keogh-review/Documents/safer-faster-better.pdf.

UK Research and Innovation (2018) *Purines for Rapid Identifcation of Stroke Mimics (PRISM)*. Available at: https://gtr.ukri.org/projects?ref=971541 (Accessed: 06/08/2018).

Vittinghoff, E. and McCulloch, C.E. (2007) 'Relaxing the rule of ten events per variable in logistic and cox regression', *American Journal of Epidemiology*, 165(6), pp. 710-718.

Walker, R.A. (2011) 'Identifying diseases that mimic strokes', *Journal of Emergency Medical Services*, 36(3), pp. 78-83.

Wardlaw, J., Murray, V., Berge, E. and del Zoppo, G. (2014) 'Thrombolysis for acute ischaemic stroke', *Cochrane Database of Systematic Reviews*, (7).

Wendt, M., Ebinger, M., Kunz, A., Rozanski, M., Waldschmidt, C., Weber, J.E., Winter, B., Koch, P.M., Nolte, C.H., Hertel, S., Ziera, T. and Audebert, H.J. (2015) 'Copeptin levels in patients with acute ischemic stroke and stroke mimics', *Stroke*, 46(9), pp. 2426-2431.

Werhahn, K.J. (2010) 'Weakness and focal sensory deficits in the postictal state', *Epilepsy & Behavior*, 19(2), pp. 138-139.

Whiteley, W., Tian, Y. and Jickling, G.C. (2012) 'Blood biomarkers in stroke: research and clinical practice', *International Journal of Stroke*, 7(5), pp. 435-9.

Whiteley, W., Wardlaw, J., Dennis, M. and Sandercock, P. (2011) 'Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: A cross-sectional study', *Journal of Neurology, Neurosurgery and Psychiatry*, 82(9), pp. 1006-10 [Online]. Available at: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/129/CN-00891129/frame.html: http://jnnp.bmj.com/content/82/9/1006.full.pdf DOI: 10.1136/jnnp.2010.235010.

Wikivoyage, P.a. (2006) *Map of North East England showing counties and major cities*. Available at: https://commons.wikimedia.org/wiki/File:North_East_England_map.png (Accessed: 06/08/2018).

Williams, T.A., Blacker, D., Arendts, G., Patrick, E., Brink, D. and Finn, J. (2017) 'Accuracy of stroke identification by paramedics in a metropolitan prehospital setting: a cohort study', *Australasian Journal of Paramedicine*, 14(2).

Winkler, D., Fluri, F., Fuhr, P., Wetzel, S., Lyrer, P.A., Ruegg, S. and Engelter, S. (2009) 'Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome', *Stroke*, 40(4), pp. 1522-1525.

Wolf, M.E., Chatzikonstantinou, A., Gruttner, J., Ebert, A.D., Walter, T., Hennerici, M.G. and Fatar, M. (2016) 'Is it acute stroke or not? - A prospective observational study from a multidisciplinary emergency department', *European Neurology*, 75(3-4), pp. 170-177.

Xian, Y., Federspiel, J.J., Cox, M., Hernandez, A.F., Kosinski, A.S., Bettger, J.P., Schulte, P., Lytle, B., Fonarow, G.C., Smith, E.E., Bhatt, D.L., Schwamm, L.H. and Peterson, E.D. (2016) 'Use of intravenous tissue plasminogen activator in patients without a stroke (Stroke Mimics): Findings from the Get With The Guidelines Stroke Registry', *Stroke*, 47, p. AWMP34.

Zhao, Y., Ji, L., Liu, J., Wu, J., Wang, Y., Shen, S., Guo, S., Jian, R., Chen, G., Wei, X., Liao, W., Kutty, S., Liao, Y. and Bin, J. (2016) 'Intensity of left atrial spontaneous echo contrast as a correlate for stroke risk stratification in patients with nonvalvular atrial fibrillation', *Scientific Reports*, 6, p. 27650.

Zinkstok, S., Engelter, S., Gensicke, H., Lyrer, P., Ringleb, P., Artto, V., Putaala, J., Haapaniemi, E., Tatlisumak, T., Chen, Y., Leys, D., Sarikaya, H., Michel, P., Odier, C., Berrouschot, J.,

Arnold, M., Heldner, M., Zini, A., Fioravanti, V., Padjen, V., Beslac-Bumbasirevic, L., Pezzini, A., Roos, Y. and Nederkoorn, P. (2013) 'Safety of thrombolysis in stroke mimics: results from a multicenter cohort study', *Stroke*, 44(4), pp. 1080-4.