Diagnostics Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project

Software with artificial intelligence-derived algorithms for analysing CT brain scans in people with a suspected acute stroke

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1 Plain English Summary

Stroke is a serious life-threatening medical condition caused by severely compromised blood supply to the brain. Restriction or stopping of the blood flow to the brain causes limited flow of oxygen and nutrients to the brain leading to the death of brain cells. Two main stroke types can be distinguished i.e., ischaemic (caused by arterial blockage, e.g. atherosclerotic plaque or blood clot) and haemorrhagic (bleeding into the brain, caused by the rupture of a blood vessel). Ischaemic and haemorrhagic strokes account for 87.1% and 12.5% of all strokes in the United Kingdom (UK), respectively. In the year 2018-2019, there were 224,172 stroke hospital admissions in the UK. Initial assessment includes computed tomography (CT) brain imaging, to identify patients with ischaemic stroke who may benefit from rapid treatment with clot-busting drugs or thrombectomy (surgical removal of the clot).

Timely and effective management of the patients with suspected stroke substantially impacts patients' outcomes. Patients should be managed by trained medical staff preferably in designated specialised stroke units. However, some patients may initially be seen in setting where some treatment options (e.g. thrombectomy and neurosurgery) are not available.

Artificial intelligence (AI) derived software currently exists which is intended to facilitate the review of CT images of the brain in conditions such as stroke. This assessment will consider the clinical- and cost-effectiveness of using AI-derived software to assist with the review of CT brain scans compared with unassisted CT brain scan review by a neuroradiologist or other healthcare practitioner, to inform diagnoses and treatment decisions for patients presenting to or attending secondary care with a suspected acute stroke.

2 Decision problem

2.1 Population

The primary population for this assessment is people presenting or attending secondary care with a suspected acute stroke, who were last known to be well within 24 hours. Within this population separate groups are considered for each research question (see Section 3)

Depending on the availability of evidence, the following subpopulation may be considered: People over the age of 80 years with small vessel disease and calcification of the cerebrovasculature.

The condition

Stroke is a serious life-threatening medical condition defined by the World Health Organization as a clinical syndrome consisting of "*rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin"*.[1] Stroke can occur without any warning and leads to interruption or restriction of the blood flow to the brain causing reduction of the flow of oxygen and nutrients to the brain and subsequently brain cell death. The effects of a stroke depend on which area of the brain is affected, the extent of damage and the time to treatment.[2]

There are two main types of stroke:

- ischaemic stroke – the most frequently occurring type of stroke resulting from reduced blood flow due to arterial occlusion. Approximately 87.1% of patients in the UK will suffer from this type of stroke. Arterial blockage can be caused by the formation of atherosclerotic plaques (fatty deposits building up in the walls of arteries). As well as narrowing the artery, making it harder for blood to pass through it, the fatty deposits can break down or become inflamed. When this happens a blood clot forms, which can block the artery. Other causes of ischaemic stroke are small vessel disease leading to vessel damage, heart conditions (i.e., atrial fibrillation, patent foramen ovale, endocarditis) or arterial dissection.[2, 3]

- haemorrhagic stroke (also referred to as intracranial haemorrhage [ICH] or cerebral haemorrhage) – accounts for approximately 12.5% of all strokes in the UK and is caused by bleeding from blood vessels in or around the brain. This type of stroke can be intracerebral (bleed within the brain) or subarachnoid (bleed on the surface of the brain in the subarachnoid space). Intracerebral haemorrhagic stroke is most associated with high blood pressure, resulting in the bursting of an artery, whereas subarachnoid haemorrhagic stroke is most frequently caused by a burst aneurysm.[2, 3]

A transient ischaemic attack (TIA), sometimes known as a mini-stroke, is differentiated from ischaemic stroke in that symptoms are time limited/self-resolving. Patients who have experienced one or more TIAs are at increased risk for ischaemic stroke.[2] The diagnosis of TIA is not considered in this assessment.

In 2018-2019, there were 224,172 stroke hospital admissions in the UK and the in-hospital crude mortality rate for 2017-2019 was reported to be 13.4%.[4] In the same year, there were over 1.2m stroke survivors in the United Kingdom (UK) with stroke prevalence (defined as patients who have had a stroke or TIA on a GP practice register) ranging from 1.77% in England to 2.28% in Scotland.[5]

Symptoms

Common symptoms include drooping of one side of the face, problems with speaking and vision, loss of sensation in an arm or leg and slurred or garbled speech. Other symptoms can include nausea, vomiting, vertigo and decreased level of consciousness.[2]

The Sentinel Stroke National Audit Programme (SSNAP), the UK national healthcare quality improvement programme, collects patient data from England, Wales and Northern Ireland and provides information on patient characteristics, outcomes, and the infrastructure of stroke services. Among 89280 stroke patients for whom data were collected between April 2019 and March 2020, the median age of patients with acute stroke in the UK was 77.[3] The risk of stroke increases with age due to continuous changes in brain arteries.[2] Females accounted for 48% of all acute stroke patients in the UK.[3]

It is estimated that approximately 90% of strokes are attributable to risk factors that can be modified during a patient's lifetime e.g., management of high blood pressure, diabetes, changes in smoking habits and addressing physical inactivity.[2] According to SSNAP, 55.1% and 22.5% of acute stroke patients in the UK suffered from hypertension and diabetes before their stroke, respectively.[3]

Diagnosis and treatment

Timely and effective management of the patients with suspected stroke substantially impacts patients' outcomes. As stroke mimics account for approximately 20 to 25% of all acute presentations, the patient history is crucial to establish the potential cause of patient's symptoms and avoid misdiagnosis.[6]

Outside the hospital setting, patients with suspected stroke should be assessed using FAST (Face Arm Speech Test) and they must be transported to the hospital as quickly as possible, preferably to a stroke unit.[7] Specialised stroke units are trained in the management of stroke patients and have access to specialist medical staff, diagnostic imaging equipment, time-sensitive procedures such as thrombectomy and thrombolysis and other services. Non-specialist units, however, may be unable to provide access to specialist medical staff or

some crucial medical procedures which can affect the timely and effective selection and treatment of patients suffering from a stroke.

In the emergency room, patients should be assessed with the Recognition of Stroke in the Emergency Room (ROSIER) scale.[7, 8] After admission, a CT or a magnetic resonance imaging (MRI) brain scan should be performed within an hour from arrival to rule out other causes of symptoms, provide information on the potential cause, show the extent of damage and decide on the best treatment option.[2] A CT scan is quick and effective method ruling out intracranial haemorrhage which is often sufficient to make thrombolysis decisions for patients with ischaemic stroke. However, the specificity of CT scan might be compromised in patients with acute ischaemia due to ongoing changes in the brain since the symptom onset.[6] Other tests may be needed, especially for patients with haemorrhagic stroke, to provide more information on the cause of stroke. In the UK, only 55.2% of acute stroke patients are scanned within 1 hour from admission, with the numbers rising to 95.5% for a scan within 12 hours from patient admission.[3] Admission directly to a stroke unit, and assessment by a stroke specialist, can lead to improved patient outcomes and reduction in complications. Patients who are seen in a specialist stroke unit are also more likely to receive more targeted secondary care.[2] Based on the SSNAP, between April 2019 and March 2020, the stroke unit was the first ward of admission for 79.9% of acute stroke patients in the UK.[3]

Some patients, however, may be initially transported to other units where direct specialist care is not available.

Patients with an ischaemic stroke can be treated with thrombolysis which uses alteplase to dissolve the clot blocking the artery in the brain.[2] The shorter the time between symptom onset and thrombolysis, the higher a patient's chance of better recovery, however, only a limited number of patients can benefit from this treatment due to the number of contraindications and potential complications that need to be considered. For stroke patients with unknown time of symptom onset, a recent systematic review showed that patients treated with alteplase thrombolysis had over three-time higher risk of symptomatic intracranial haemorrhage (sICH; a side effect of thrombolysis) when compared to patients receiving conservative medical treatment. There was no increase in the risk of death at three months and patients had a similar likelihood of functional independence.[9]

Some ischaemic stroke patients may benefit from thrombectomy (i.e., extraction of arterial obstruction with a device). Thrombectomy is considered if the obstruction is present in a large artery[10] and has been shown to be superior to best medical therapy alone (e.g. thrombolysis alone) for patients with anterior circulation large artery occlusion.[6] In patients with an ischaemic stroke, thrombolysis can be administered before mechanical thrombectomy without an increase in the incidence of sICH or mortality at 90 days when compared to thrombectomy alone. Similarly, there is no difference between treatments in

the rates of successful recanalization or the level of patients' functional independence at 90 days.[11]

Patients with haemorrhagic stroke require intensive blood pressure-lowering medications or reversal of antithrombotic medications at the early stages of their treatment. Patients may undergo surgery to seal a burst aneurysm or relieve the pressure on the brain. Severe headaches can be addressed with pain relief medications.[2]

More information regarding the patient pathway, available treatments, and patient eligibility for treatment in the NHS setting is provided in Section 2.3.

2.2 Intervention technologies

Over recent years, a number of software products with AI-derived algorithms have been developed, which are intended to facilitate the review of CT images of the brain in conditions such as stroke. These products are not intended to provide a diagnosis, but rather to support the review of scans, reporting by a radiologist and prioritisation of critical cases.

For patients with suspected stroke, software using AI-derived algorithms may be a useful tool in the early stages of the treatment pathway, particularly where neuroradiologist assessment of the CT images is not directly available. The use of AI-derived algorithms may potentially speed up the process of reviewing CT scans by identifying, quantifying, and notifying about clinically relevant brain structures related to acute stroke. Highlighting stroke-related changes in the patient' brain may assist in confirming a stroke, and along with other patient information, expedite the patient transfer and support assessments of the suitability of time-sensitive treatments such as thrombolysis and thrombectomy leading to improvement of patient outcomes. Other potential benefits include improved report turnaround time and enabling rapid review of scans by a multi-site clinical team.

These software products are typically designed to be incorporated into standard radiology CT workstations. This means they can work with existing forms of brain imaging (including non-contrast CT [non-enhanced], CT angiography [CTA] and CT perfusion [CTP] imaging), radiology information systems (RIS) and picture archiving and communication systems (PACS). They are typically hosted on a web cloud which is separate from image exchange portals used to transfer images between care providers.

The Royal College of Radiologists published a position statement[12] guidance (Integrating artificial intelligence with the radiology reporting workflows [RIS and PACS]).[13] The guidance recommends that:

- *'AI must be integrated in reporting (radiology information system [RIS] and picture archiving and communication system [PACS]) workflows seamlessly and in a way that does not add extra burden to radiologists.*
- *The accuracy of the AI algorithms must be clearly declared for radiologists and others making decisions on patient management.*
- *AI findings must be communicated to the RIS via existing, widely used global technical standards (HL7).*
- *AI findings must be communicated to the PACS using existing, widely used global technical standards (DICOM).*
- *The workflow must be robust enough to ensure AI analysis is complete and available on PACS before a human reporter starts image interpretation.'*[13]

In March 2020, NICE published Medtech innovation briefing 207 (MIB207; "Artificial intelligence for analysing CT brain scans")[14] describing AI-derived software for CT brain scans. Based on MIB207, "*the intended place in therapy would be to support radiologists in secondary care when they are reviewing CT brain scans of people with suspected brain abnormalities. The technology may be of most benefit when images are not first reviewed by neuroradiologists*."[14]

Several companies offer software with AI-derived algorithms for analysing CT brain scans in people with a suspected acute stroke. Some companies offer software that can be used to analyse non-enhanced, CTA and CTP scans (or have agreements between companies to offer their algorithms as a package), whereas others have software that can only analyse one of these types of scans. Some software packages do not have a dedicated platform through which they are delivered but may be housed on multivendor platforms for example Blackford analysis.

These technologies are classed as medical devices and require CE mark. Details of the technologies to be considered in this assessment are provided below. Where less detail is given, this is because only information available in the public domain was able to be used.

Table 1. Summary of types of CT scans analysed by AI-derived software platforms included in this assessment

Platform	Available to the NHS	Type of CT scan analysed		
		Non-enhanced CT	CTA	CTP
icobrain ct	✓			✓
Aidoc	✓	✓	✓	
Aidoc + icobrain	NYD	✓	✓	✓
RapidAI	✓	✓*	✓	✓
e-stroke	✓	✓*	✓	✓
Viz	✓	✓	✓	✓

qER**	NYD	✓		
Zebra-Med	TBC	✓		
CT Perfusion 4D	TBC			✓
Brainscan	TBC	✓		
Cercare stroke**	NYD			✓
Cina head**	✓	✓*	✓	
Accipio**	✓	✓	✓	
Biomind	TBC	✓		
CT- computed tomography, CTA- CT angiography, CTP- CT perfusion *Gives ASPECTS score by assessing non-enhanced CT, NYD- Not yet deployed, **Provided through a multivendor platform, Blackford analysis.				

icobrain ct

icobrain ct (Icometrix) is a CE marked (class 1 medical device) neuroimaging platform which uses AI-derived algorithms to detect abnormalities in brain CT scans. icobrain ct can generate 2 output reports related to stroke diagnosis:

- Report 1, from icobrain ctp (ct perfusion), details a quantitative assessment of perfusion in the brain based on a CT scan done with contrast. It analyses the flow of blood in areas of the brain to determine the presence of potentially salvageable tissues in ischaemic stroke. The analysis includes a calculation of abnormality in parameters such as mean transit time (MTT), cerebral blood flow (CBF), cerebral blood volume (CBV) and time to maximum (Tmax) of residue function.

- Report 2, from icobrain tbi (traumatic brain injury), can give a quantitative assessment of intracranial haemorrhage (ICH) based on a non-enhanced CT scan. This report also has application in traumatic brain injury. Some of the non-contrast CT parameters measured include midline shift and asymmetry index between the left and right lateral ventricle.

The company notes that its AI-derived neuroimaging platform integrates with existing RIS and PACS. The software is intended for automatic labelling, visualization, and volumetric quantification of segmentable brain structures from a set of CT images. It receives digital images as input and generates an electronic report on quantitative parameters and annotated images. Results can be viewed as visual reports through DICOM (digital imaging and communication in medicine) output images, email notifications and on a web browser. The report highlights stroke-related changes that guide clinician diagnosis. Data transfer from and into the PACS is done securely over a software icobridge, installed on site. Icobrain ct has had 2 major releases, versions 4.0 and 5.0. The company notes that performance of icobrain in detecting ICH and for CT perfusion analysis has been tested on a series of scenarios that cover specific aspects of the software performance. Icobrain ct algorithms send and receive information over a secure cloud 'icometrix'. icometrix is ISO13485 and ISO27001 certified and GDPR and HIPAA compliant for privacy and security.

The company provides a training manual for health professionals which gives guidance on how to use the software and interpret reports. Customer support is also available from the company. Prior to deployment in clinical practice the company carries out a clinical and technical test phase. Icobrain ct is currently a self-certified class 1 medical device under the Medical Device Directive, the company notes that it will be up classified to a class 2a medical device under the Medical Device Regulation, in line with the transition from the Medical Device Directive to the Medical Device Regulation.

Aidoc ICH, Aidoc LVO, Aidoc mobile

The Aidoc software (also called "BriefCase" [Aidoc]) is a CE marked (class 1 medical device) AI triage and notification platform. This neuroimaging platform uses AI-derived algorithms to detect abnormalities in brain CT scans. Algorithms related to stroke diagnosis include:

- Aidoc ICH for detecting suspected intracranial haemorrhage on non-contrast head CT
- Aidoc LVO for detecting suspected large vessel occlusions on CT angiography

The third component of the platform relevant to stroke diagnosis is Aidoc mobile, which is for communication between clinical stakeholders in the stroke pathway to facilitate peer review.

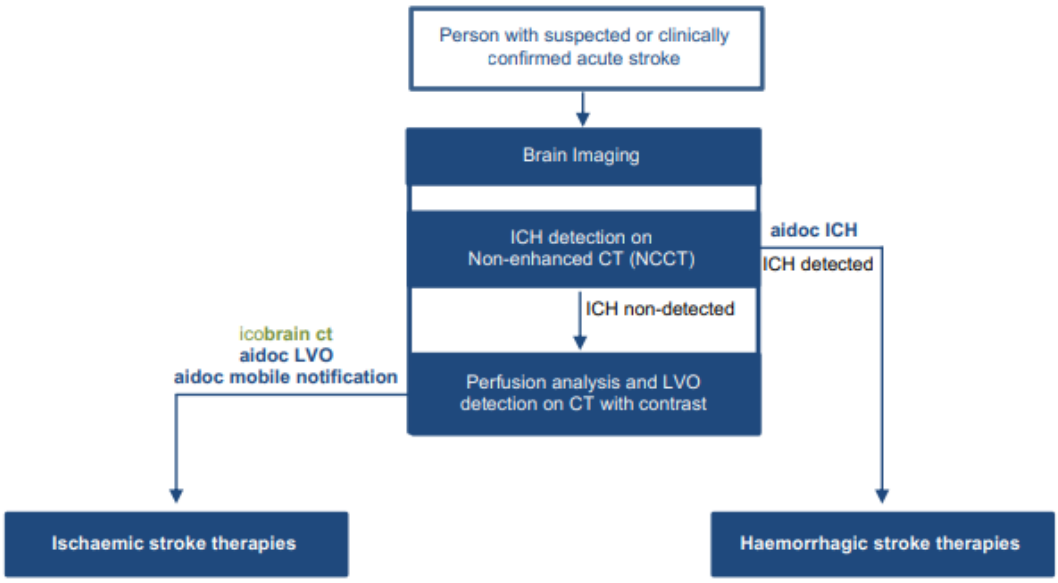
The company notes that its software can integrate with existing radiology workstation including PACS, reporting system and radiology workflow solutions. The platform can prioritise worklist, triage, and generate notification on suspected stroke cases. Analysis done by the AI-derived software is intended to supplement CT scan review by a neuroradiologist or stroke specialist.

The company provides an initial product training which lasts around 30 minutes and where necessary additional training on specific workflows can be provided. A recurring annual training is also available to review new features, enhancements, and algorithms. Prior to deployment of the software on a site, the company through its AI operations centre carries out an automated performance assessment. Aidoc is ISO13485 and ISO27001 certified. The Aidoc software is currently a self-certified class 1 medical device under the Medical Device Directive, the company notes that it will be up classified to a class 2a medical device under the Medical Device Regulation, in line with the transition from the Medical Device Directive to the Medical Device Regulation.

Icometrix and Aidoc 'comprehensive stroke solution'

Aidoc and icometrix have partnered to provide a stroke solution in which the Aidoc software detects intracranial haemorrhage and large vessel occlusion and the icobrain software is used for CT perfusion analysis to detect ischaemic stroke. Figure 1 shows how the technologies are intended to be implemented in clinical practice.

Figure 1 Icometrix and Aidoc 'comprehensive stroke solution' pathway



Rapid ASPECTS, Rapid ICH, Rapid CTA, Rapid LVO, Rapid CTP

RapidAI (Ischemaview) is a CE marked (class 2a medical device) neuroimaging platform which uses AI-derived software for detecting abnormalities in brain CT scans. The CT algorithms relevant to stroke diagnosis are:

- Rapid ICH is an image processing software that analyses non-enhanced CT head scans to detect, and flag suspected intracranial haemorrhage. Cases with suspected findings can be notified through email and the mobile application. The notification includes compressed images that are for informational purposes only and not intended to be diagnostic. The notified clinician is responsible for viewing non-compressed images on a diagnostic viewer and carrying out necessary patient evaluation.

- Rapid CTA is an image processing software that analyses head CT angiograms scans to provide neurologic vasculature maps with indications of hemispheric differences in the intracranial ICA/MCA (internal carotid artery/ middle cerebral artery) region which may indicate a large vessel occlusion.

- Rapid LVO is an image processing software that analyses head CT angiograms scans to highlight and notify cases with suspected large vessel occlusion

- Rapid CTP enables the assessment of salvageable brain tissue through the delivery of quantified and colour-coded CT perfusion maps that identify brain regions with reduced cerebral blood flow, volume, and transit time that exceed pre-specified thresholds. Imaging datasets acquired from CT or Cone Beam Computed

Tomography (CBCT) or MR Perfusion and Mismatch, MR Diffusion, and CT/MR Angiography are analysed to measure parameters that determine suitability for thrombectomy.

- RAPID ASPECTS is not intended for the primary interpretation of CT images. It assists the clinician in evaluating patients presenting for diagnostic imaging with known MCA or ICA occlusion, to assess the extent of disease on non-contrast CT scans. Extent of disease refers to the number of ASPECTS (Alberta Stroke Program Early CT Score) regions affected. Image data and AI analysis of morphological features is used to generate a single ASPECT score. This score is useful in characterizing early signs of brain ischaemia, areas of irreversible tissue injury and to help the clinician assess patient eligibility for thrombectomy or thrombolysis.

The RapidAI platform runs on a standard computer or a virtual platform, such as VMware, and can be used to perform image viewing, processing, and analysis. The software receives DICOM compliant images as input primarily CT, CTA, CBCT and Magnetic Resonance (MR). Results from on Rapid platform can be viewed as visual reports through PACS, email notifications and the Rapid mobile app. Notifications have a sound option for positive cases and can be set to user defined thresholds to enable prioritisation. Results from multiple sites can be viewed and organised in one location. RapidAI is ISO certified and complies with GDPR and data security requirements.

The company provides training which includes online role-based product training, virtual instructor-led sessions led by clinical experts and performance support content.

e-ASPECTS, e-CTP, e-CTA

The e-Stroke platform (Brainomix) is a CE marked (class 2a medical device) neuroimaging platform that utilises AI-derived software for detecting anomalies in brain CT scans. The platform includes the following algorithms relevant to stroke diagnosis:

- e-ASPECTS which analyses non-contrast CT scans for clot detection, signs of hypodensity and generates a heat map of regional ischaemic change, volume of the change, and an automatic ASPECTS score.

- e-CTP which analyses CT perfusion scans to generate perfusion summary maps, report parameters such as mismatch volume and ratio, hypoperfusion intensity ratio, and assesses eligibility for mechanical thrombectomy.

- e-CTA which analyses CT angiogram scans to detect the location of large vessel occlusions and to generate a CT collateral score which is used to assesses eligibility for mechanical thrombectomy.

The software integrates with current imaging systems and results can be viewed as visual reports through DICOM output images, email notifications and a web browser.

Viz

The Viz platform (Viz.ai) is a CE marked (class 1 medical device) software which uses static AI-derived algorithms to detect abnormalities in brain scans in clinical practice. The algorithms relevant to stroke detection include:

- Viz LVO which analyses CT angiogram images of the brain and sends notification to the clinician if a suspected large vessel occlusion has been detected. Notifications include compressed images that can be previewed for information purposes only. They are not intended to be diagnostic. The notified clinician is responsible for viewing non-compressed images on a diagnostic viewer and carrying out necessary patient evaluation.

- Viz ICH which analyses non-contrast CT images of the brain and sends notification to the clinician if a suspected intracranial haemorrhage has been detected.

- Viz CTP has communication and analysis capabilities for CT perfusion scans. The analysis includes the calculation of parameters related to tissue perfusion and tissue blood volume.

The company notes that the Viz platform integrates with currently available CT scanners and is designed to receive DICOM images which can be transferred securely to Viz.ai's GDPR-compliant Amazon Web Services cloud. Within the cloud, Viz.ai will analyse the imaging data for specific neurovascular disease. The platform can be used by hospital networks and trained clinicians.

The Viz platform is GDPR/HIPAA compliant and has ISO and SOC-2 certifications. Viz is currently a self-certified class 1 medical device under the Medical Device Directive, the company notes that it will be up classified to a class 2a medical device under the Medical Device Regulation, in line with the transition from the Medical Device Directive to the Medical Device Regulation.

qER

qER (Qure.ai) is a CE marked triage and notification tool that detects and quantifies a range of brain abnormalities intracerebral bleeds and their subtypes, infarcts, mass effect, midline shift and cranial fractures following non-contrast CT imaging. The software populates a radiology reporting template with preliminary findings, patient prioritisation and alert systems including mobile notifications. It integrates with current imaging systems.

Zebra triage

Zebra-Med (Zebra Medical Vision) is a CE marked (class 1 medical device) software that detects and annotates intracranial haemorrhage after non-contrast CT imaging and automates patient prioritisation and a real-time alert system. It integrates with the current imaging worklist and viewer with an accompanying alert widget.

CT Perfusion 4D Neuro

CT Perfusion 4D (GE Healthcare) is a CE marked medical device for CT perfusion image analysis of images obtained by cine imaging (in the head and body) after the intravenous injection of contrast. It produces image data and generates information regarding changes in image intensity over time and in calculation of the various perfusion-related parameters (including regional blood flow, regional blood volume, mean transit time and capillary permeability).

Brainscan

The Brainscan system is a CE marked AI-derived platform that enables automatic detection and classification of pathological changes occurring in CT examinations of the brain.

Cercare stroke

Cercare stroke (Cercare Medical) is a CE marked AI enabled stroke CT and MRI imaging software. The technology uses inputs from perfusion maps and additional maps of oxygen extraction and metabolism to provide an overview of brain tissues status in stroke.

CINA head

CINA head (Avicenna) uses CE marked (class 1 medical device) artificial intelligence software for detecting abnormalities in brain CT scans. The algorithms in CINA head include:

- CINA-ICH which identifies suspected intracranial haemorrhage on non-contrast CT scans and prioritises them on the radiologist's worklist
- CINA LVO detects and prioritises the review of suspected large vessel occlusions on CT angiography.
- CINA ASPECTS analyses non-contrast CT and creates heat maps that indicate signs of hypodensity which help characterise early ischaemic brain tissue injury

ACCIPIO

Accipio suite (MaxQ AI) is a CE marked (class 2a medical device) AI-derived software that can identify, analyse, prioritise, annotate and triage both positive and negative findings of suspected intracranial haemorrhage on non-contrast CT scans and large vessel occlusions on contrast CT scans.

Biomind

Biomind (Biomind.ai) is a CE marked (class not available publicly) AI-derived software used for detecting the location of intracerebral haemorrhage on CT scans and assessing its severity.

2.3 Care pathway

Stroke care service provision

The NHS Long Term Plan[15] identifies stroke as a clinical priority and sets out (section 3.78) the NHS's ambition to support the national scaling of technology that will assist the expansion of life-changing treatments to more patients, which includes CT perfusion scans to assess the reversibility of brain damage, improved access to MRI scanning and the potential use of artificial intelligence in the interpretation of CT and MRI scans to support clinical decisions regarding suitability for thrombolysis and thrombectomy.

The National Stroke Service Model: Integrated Stroke Delivery Networks[16] outlines best practices for stroke care, people with a suspected stroke should typically receive care within 4 hours in a hospital with a:

- Comprehensive stroke centre that provides hyper-acute, acute and inpatient rehabilitation including thrombectomy and neurosurgery services or in an
- Acute stroke centre which provides hyper-acute, acute and inpatient rehabilitation, but *excluding thrombectomy and neurosurgery*. All acute stroke centres are expected to have an intra hospital thrombectomy transfer pathway to transfer patients from acute stroke centres to comprehensive stroke centres.

Hyper-acute stroke care usually covers the first 72 hours after a person is admitted. Services provided in the hyperacute phase include specialist clinical assessment, urgent imaging and skilled clinical interpretation of images, delivery of intravenous thrombolysis 24 hours a day, 7 days a week and transfer or treatment for thrombectomy. Imaging ensures that appropriate diagnosis is made, and time-dependent interventions are delivered. The guidance describes an optimal stroke imaging pathway (see Figure 2).

Initial assessment

The diagnosis and initial management of patients with suspected stroke are discussed in National Institute for Health and Care Excellence (NICE) guideline NG128 ("Stroke and transient ischaemic attack in over 16s: diagnosis and initial management").[7] For a diagnosis of stroke or TIA, patients with sudden onset of neurological symptoms outside of hospital should be assessed using e.g. FAST (Face Arm Speech Test) tool and check for a potential episode of hypoglycaemia. For patients admitted to the emergency department, the early diagnosis should be established using e.g. a ROSIER tool.[7]

The NG128 recommends "*Admit everyone with suspected stroke directly to a specialist acute stroke unit after initial assessment, from either the community, the emergency department, or outpatient clinics. (An acute stroke unit is a discrete area in the hospital that is staffed by a specialist stroke multidisciplinary team. It has access to equipment for monitoring and rehabilitating patients. Regular multidisciplinary team meetings occur for goal setting.)"*[7] Similarly, Quality standard QS2 ("Stroke in adults") published by NICE[1] states "*Adults presenting at an accident and emergency (A&E) department with suspected stroke are admitted to a specialist acute stroke unit within 4 hours of arrival.*"

For patients with an initial diagnosis of acute stroke and an indication of prompt brain imaging, NG128[7] recommends immediate (i.e. "*ideally the next slot and definitely within 1 hour, whichever is sooner*") brain imaging with a non-enhanced CT to rule out or confirm intracranial haemorrhage, if any of the following apply:

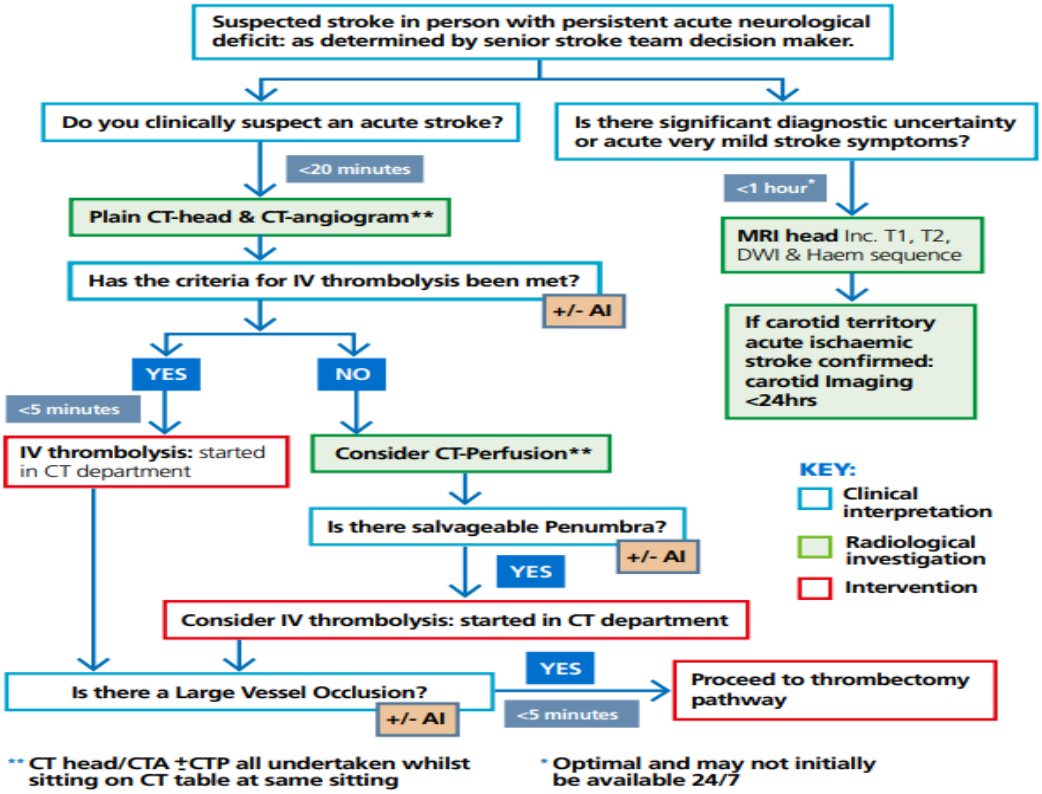
- indications for thrombolysis or thrombectomy,
- on anticoagulant treatment,
- a known bleeding tendency,
- a depressed level of consciousness (Glasgow Coma Score below 13),
- unexplained progressive or fluctuating symptoms,
- papilloedema, neck stiffness or fever,
- severe headache at onset of stroke symptoms.

For patients with an indication to thrombectomy, CT with contrast angiography should be performed following an initial non-enhanced CT scan to confirm the presence of occlusion and/or clot. Addition of CT perfusion imaging, or MR equivalent, is recommended if thrombectomy is indicated beyond 6 hours of symptom onset in order to assess potential salvage of brain tissue.[7]

Patients with suspected acute stroke without indication for immediate brain imaging should be scanned as soon as possible and within 24 hours of symptom onset.[7]

The National Stroke Service Model guidance[16] describes an optimal stroke imaging pathway (see Figure 2) and recommends that stroke imaging, interpretation and transfer decisions are made within 20 minutes of patient's arrival.

Figure 2 National Stroke Service Model optimal imaging pathway



Source: The National Stroke Service Model: Integrated Stroke delivery Networks[16]

Treatment

Initially, patients with acute stroke must have their blood glucose concentration maintained and can be offered supplemental oxygen therapy if oxygen saturation drops below 95%.[7] The treatment options for patients with suspected or confirmed ischaemic or haemorrhagic stroke are summarised below.

Ischaemic stroke

For patients with suspected or clinically confirmed ischaemic stroke, NG128[7] and technology appraisal guidance 264 (TA264; Alteplase for treating acute ischaemic stroke)[17] recommends thrombolysis with alteplase (within its marketing authorisation) if:

- treatment is started as early as possible within 4.5 hours of onset of stroke symptoms,
- and intracranial haemorrhage has been excluded by appropriate imaging techniques.

Alteplase should be administered in a well organised stroke service with appropriately trained staff to deliver thrombolysis and monitor for any complications, nurse staff trained in acute stroke care and immediate access to brain imaging with professionals trained to interpret images. The procedure can also be carried out in the emergency department if staff are appropriately trained and supported and patients can be managed after the procedure in an acute stroke service.[7]

Thrombectomy for ischaemic stroke is recommended by NICE with more information available in interventional procedures guidance 548 (IPG548; "Mechanical clot retrieval for treating acute ischaemic stroke Interventional procedures guidance").[18]

For patients with acute ischaemic stroke and confirmed occlusion of the proximal anterior circulation demonstrated by CT or MR angiography, thrombectomy together with intravenous thrombolysis (if not contraindicated and within the licensed time window) should be offered as soon as possible and within 6 hours of symptom onset.[7] Thrombectomy alone should be offered for the same patient population (acute ischaemic stroke and confirmed occlusion of the proximal anterior circulation demonstrated by CT or MR angiography) last known to be well between 6 to 24 hours (including wake-up strokes), with the potential to salvage brain tissue as shown by CT perfusion or diffusion-weighted MRI sequence.[7]

For patients last known to be well up to 24 hours (including wake-up strokes) with acute ischaemic stroke and who have confirmed occlusion of the proximal posterior circulation demonstrated by CT or MR angiography and the potential salvage brain tissue (as shown by CT perfusion or diffusion-weighted MRI sequence), thrombectomy is recommended together with intravenous thrombolysis.[7]

Patients with ischaemic stroke are recommended to receive pharmacological treatment i.e., aspirin (or an alternative antiplatelet agent if there is intolerance to aspirin) within 24 hours. Anticoagulant therapy with heparin and then warfarin is recommended for people diagnosed with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage).[7]

Haemorrhagic stroke

Surgical intervention following primary intracerebral haemorrhage can be considered for previously fit people. Initial medical treatment, instead of surgical intervention, should be offered for patients with:

- small deep haemorrhages,
- lobar haemorrhage without either hydrocephalus or rapid neurological deterioration,
- a large haemorrhage and significant comorbidities before the stroke,
- a score on the Glasgow Coma Scale of below 8 unless this is because of hydrocephalus,
- posterior fossa haemorrhage.[7]

The NG128 recommends a reversal of anticoagulation treatment using a combination of prothrombin complex concentrate and intravenous vitamin K, in people with a primary intracerebral haemorrhage who were receiving warfarin before their stroke.[7]

3 Objectives

The overall objective of this assessment is to evaluate the clinical and cost effectiveness of using AI-derived software to support the review of CT brain scans in acute stroke, in the NHS setting. The following decision questions have been defined to address the stated objective:

1. Does AI-derived-software-assisted review of non-enhanced CT brain scans for guiding thrombolysis treatment decisions for people with suspected acute stroke represent a clinically and cost-effective use of NHS resources?

2a. Does AI-derived-software-assisted review of CT angiography brain scans for guiding mechanical thrombectomy treatment decisions for people with an ischaemic stroke represent a clinically and cost-effective use of NHS resources?

2b. Does AI-derived-software-assisted review of CT perfusion brain scans for guiding mechanical thrombectomy treatment decisions for people with an ischaemic stroke after a CT angiography brain scan represent a clinically and cost-effective use of NHS resources?

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[19], NICE Diagnostics Assessment Programme manual[20] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[21]

4.1 Inclusion and exclusion criteria

Separate inclusion criteria were developed for each of the decision questions and these are summarised in Table 2.

4.2 Search strategy

Search strategies will be undertaken to identify interventions using AI-derived software to diagnose acute stroke, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[19, 21] Searches for studies for costs and quality of life will be developed separately.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase EMTREE), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference manager software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of

sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords and thesaurus terms will be adapted according to the configuration of each database.

- MEDLINE (Ovid)
- MEDLINE In-Process Citations (Ovid)
- MEDLINE Daily Update (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Science Citation Index (SCI) (Web of Science)
- Database of Abstracts of Reviews of Effects (DARE) (Internet) (https://www.crd.york.ac.uk/CRDWeb/)
- Health Technology Assessment Database (HTA) (Internet) (https://www.crd.york.ac.uk/CRDWeb/)
- KSR Evidence (KSR Ltd)
- Epistemonikos (Internet) (https://www.epistemonikos.org/)
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication (Internet) http://www.inahta.org/
- NIHR Health Technology Assessment Programme (Internet) (https://www.nihr.ac.uk/)
- Aggressive Research Intelligence Facility (ARIF) database (Internet) (http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) (http://www.crd.york.ac.uk/prospero/)
- International Platform of Registered Systematic Review and Meta-analysis Protocols (Internet) (Home - INPLASY)
- Latin American and Caribbean Health Sciences Literature (LILACS) (Internet) (http://regional.bvsalud.org/php/index.php?lang=en)

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov/)
- EU Clinical Trials Register (Internet) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet) (http://www.who.int/ictrp/en/
- ScanMedicine (Internet) (https://scanmedicine.com/)

To identify conference proceedings, searches in Embase will not be restricted to exclude conference abstracts. In addition, a search will be undertaken of the following specific conference proceedings resources:

- Northern Light Life Sciences Conference Abstracts (Ovid)
- Conference Proceedings Citation Index (Web of Science)

Key conference proceedings, not indexed in either Embase, Northern Light or Web of Science, and identified in consultation with clinical experts may also be screened for the last five years.

No restrictions on language, publication status or date will be applied. Searches will take into account generic and other product names for the intervention. An example search strategy is presented in Appendix 1. This may be adapted following consultation with clinical experts.

The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist based on the CADTH Peer Review checklist.[22]

Table 2: Inclusion criteria

Decision question 1	**Is the use of AI-derived software to assist review of non-enhanced CT brain scans to guide thrombolysis treatment decisions for people with suspected acute stroke a clinically effective intervention?**	
Research question	**What is the diagnostic performance of AI-derived-software-assisted review of plain CT brain scans to rule-out ICH and to rule-in ischaemic stroke in people with suspected acute stroke?**	**What are the clinical effects of using AI-derived-software-assisted review of plain CT brain scans to guide thrombolysis treatment decisions in people with suspected acute stroke?**
Participants:	Adults (≥18 years old) attending a secondary care stroke centre with suspected acute stroke and who were last known to be well within 24 hours	
Interventions (index test):	AI-derived-software-assisted review of plain CT brain scan by a healthcare professional other than a neuroradiologist	AI-derived-software-assisted plain CT brain scan review by a neuroradiologist or other healthcare professional
Comparators:	AI-derived-software-assisted plain CT brain scan review by a healthcare professional other than a neuroradiologist, using a different AI-derived technology, or unassisted plain CT brain scan review by a healthcare professional other than a neuroradiologist	Unassisted plain CT brain scan review by a neuroradiologist or other healthcare professional
Reference standard:	Unassisted plain CT brain scan review by a neuroradiologist, or by a consensus panel	Not applicable
Outcomes:	Test accuracy (the numbers of true positive, false negative, false positive and true negative test results), for the target conditions ICH and ischaemic stroke. *Where reported, information will also be extracted on technical failure rates, time to intervention and ease of use/acceptability to clinicians	Clinical/patient-perceived outcomes: mortality, function (e.g. modified Rankin score), health-related quality of life, adverse events (e.g. bleed subsequent to thrombolysis), length of hospital stay. *Where reported, information will be extracted on technical failure rates, time to thrombolysis/rate of thrombolysis within the clinically appropriate time window, time in emergency department prior to admission or discharge and ease of use/acceptability to clinicians
Study design:	Diagnostic cohort studies	All comparative study designs; study designs will be included in a hierarchical manner (RCTs, CCTs, observational studies), i.e. CCTs and

		observational studies will only be considered for inclusion where no RCTs are identified, or where there are concerns about the applicability (e.g. non-UK settings) or risk of bias for identified RCTs
Decision question 2a	**Is the use of AI-derived software to assist review of CT angiography brain scans for guiding mechanical thrombectomy treatment decisions for people with an ischaemic stroke a clinically effective intervention?**	
Research question	**What is the diagnostic performance of AI-derived-software-assisted review of CT angiography brain scans to guide thrombolysis treatment decisions in people with confirmed ischaemic acute stroke?**	**What are the clinical effects of using AI-derived-software-assisted review of CT angiography to guide mechanical thrombectomy treatment decisions in people with confirmed ischaemic stroke?**
Participants:	Adults (≥18 years old) attending a secondary care stroke centre with acute ischaemic stroke, who were last known to be well within 6 hours	
Interventions (index test):	AI-derived-software-assisted CT angiography brain scan review by a healthcare professional other than a neuroradiologist	AI-derived-software-assisted CT angiography brain scan review by a neuroradiologist or other healthcare professional
Comparators:	AI-derived-software-assisted CT angiography brain scan review by a healthcare professional other than a neuroradiologist, using a different AI-derived technology, or unassisted CT angiography brain scan review by a healthcare professional other than a neuroradiologist	Unassisted CT angiography brain scan review by a neuroradiologist or other healthcare professional
Reference standard:	Unassisted CT angiography scan review by a neuroradiologist, or by a consensus panel	Not applicable
Outcomes:	Test accuracy (the numbers of true positive, false negative, false positive and true negative test results) for the target condition (large vessel occlusion/occlusion of the proximal anterior circulation) *Where reported, information will also be extracted on technical failure rates, time to start of interventional	Clinical/patient-perceived outcomes: mortality, function (e.g. modified Rankin score), health-related quality of life, procedure-related adverse events (e.g. bleed subsequent to thrombolysis), length of hospital stay. *Where reported, information will be extracted on technical failure rates, time to start of interventional procedure (insertion of catheter),

	procedure (insertion of catheter) and ease of use/acceptability to clinicians	reperfusion rates and ease of use/acceptability to clinicians
Study design:	Diagnostic cohort studies	All comparative study designs; study designs will be included in a hierarchical manner (RCTs, CCTs, observational studies), i.e. CCTs and observational studies will only be considered for inclusion where no RCTs are identified, or where there are concerns about the applicability (e.g. non-UK settings) or risk of bias for identified RCTs
Decision question 2b	**Is the use of AI-derived software-assisted review of CT perfusion brain scans to guide mechanical thrombectomy treatment decisions for people with an ischaemic stroke, after a CT angiography brain scan, a clinically effective intervention?**	
Research question	**What is the diagnostic performance of AI-derived-software-assisted review of CT angiography and CT perfusion brain scans to guide thrombolysis treatment decisions in people with confirmed ischaemic acute stroke?**	**What are the clinical effects of using AI-derived software-assisted review of CT angiography and CT perfusion brain scans to guide mechanical thrombectomy treatment decisions in people with confirmed ischaemic stroke?**
Participants:	Adults (≥18 years old) attending a secondary care stroke centre with suspected acute stroke, who were last known to be well more than 6 hours previously, but within 24 hours, and in whom ischaemic stroke has been confirmed on plain CT	
Interventions (index test):	AI-derived-software-assisted CT angiography and CT perfusion brain scan review by a healthcare professional other than a neuroradiologist	1. AI-derived-software-assisted CT angiography and AI-derived-software-assisted CT perfusion brain scan review by a neuroradiologist or other healthcare professional 2. Unassisted CT angiography and AI-derived-software-assisted CT perfusion brain scan review by a neuroradiologist or other healthcare professional
Comparators:	AI-derived-software-assisted CT angiography and CT perfusion brain scan review by a healthcare professional other than a neuroradiologist, using a different AI-derived technology, or unassisted CT angiography and CT perfusion brain scan review by a healthcare professional other than a neuroradiologist	Unassisted CT angiography brain scan review by a neuroradiologist or other healthcare professional and unassisted CT perfusion brain scan review by a neuroradiologist
Reference standard:	Unassisted CT angiography and CT perfusion scan review by a	Not applicable

	neuroradiologist, or by a consensus panel	
Outcomes:	Test accuracy (the numbers of true positive, false negative, false positive and true negative test results) for the target conditions (large vessel occlusion/occlusion of the proximal anterior circulation for CT angiography and presence of salvageable tissue for CT perfusion) *Where reported, information will also be extracted on technical failure rates, time to start of interventional procedure (insertion of catheter) and ease of use/acceptability to clinicians	Clinical/patient-perceived outcomes: mortality, function (e.g. modified Rankin score), health-related quality of life, procedure-related adverse events (e.g. bleed subsequent to thrombolysis), length of hospital stay. *Where reported, information will be extracted on technical failure rates, time to start of interventional procedure (insertion of catheter), reperfusion rates and ease of use/acceptability to clinicians
Study design:	Diagnostic cohort studies	All comparative study designs; study designs will be included in a hierarchical manner (RCTs, CCTs, observational studies), i.e. CCTs and observational studies will only be considered for inclusion where no RCTs are identified, or where there are concerns about the applicability (e.g. non-UK settings) or risk of bias for identified RCTs
*Secondary outcomes, which are not sufficient to inform decision making in the absence of higher-level outcomes data		

Comparative studies, which report secondary outcomes only (time to intervention and acceptability to clinicians), will be included, in order to maximise the available information for these outcomes. However, it should be noted that these outcomes alone are not sufficient to inform meaningful estimates of the clinical and cost effectiveness of software using AI-derived algorithms for analysing CT brain scans in people with a suspected acute stroke; because it is possible, for example, for the use of such software to reduce time to intervention whilst also being associated with poorer clinical outcomes, secondary outcome data are only useful for decision making when combined with data on higher-level outcomes (clinical outcomes or measures of diagnostic performance).

If all comparative studies identified are studies conducted in non-UK settings or in highly specialised NHS settings only, single arm, non-comparative studies, conducted in the UK NHS may be used to gauge the extent to which studies conducted in non-UK settings or in highly specialised NHS settings may be applicable to the wider UK NHS.

4.3 Review methods

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participant characteristics, details of the AI-derived software (e.g. manufacturer), details of comparator (i.e. who reviewed the scans), clinical outcomes (e.g. morbidity, mortality, etc.), and test performance outcome measures. Data will be extracted by one reviewer using the data extraction forms. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment

The methodological quality of included RCTs will be assessed using the revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2).[23] Diagnostic accuracy studies will be assessed using QUADAS-2.[24] The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Where sufficient data are available the results of quality assessment may be used to inform stratified meta-analyses in order to explore the impact of individual components of study quality upon the findings of the review. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Data synthesis

If available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.[25-27] If more than one RCT evaluates the same clinical outcome in patients assessed with the same intervention (AI-assisted CT brain scan review) and comparator (non-AI-assisted CT brain scan review), then data will be pooled on treatment effect (e.g. hazard ratio, odds ratio, relative risk, weighted mean difference). The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs. Any estimates of the relative accuracy/effectiveness of different AI-derived software and/or algorithm will be derived from direct, within study comparisons.

Depending on the availability of evidence, the following subpopulation may be considered: People over the age of 80 years with small vessel disease and calcification of the cerebrovasculature

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed and by type of AI-derived software and/or algorithm. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

5 Methods for synthesising evidence of cost-effectiveness

5.1 Identifying and reviewing published cost-effectiveness studies

Search strategy

Literature searches will be performed to identify published economic evaluations, cost studies and utility studies. A methodological study design filter to identify cost and economic studies in databases that are not health economic specific will be included in the search strategy for economic evaluations. Relevant economic evaluations, utility studies and cost studies will be searched for using the following databases and resources:

- NHS Economic Evaluation Database (NHS EED) (Internet) (https://www.crd.york.ac.uk/CRDWeb/)
- MEDLINE (Ovid)
- MEDLINE In-Process Citations (Ovid)
- MEDLINE Daily Update (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- EconLit (EBSCO)
- CEA Registry (http://www.cearegistry.org)
- Research Papers in Economics (RePEc) (http://repec.org/)

Where applicable, a summary with the results and the methodological quality of relevant studies will be provided. Methodological quality will be assessed using the Drummond checklist.[28]

Exploration of the literature regarding published utility and cost studies will be performed. The intention of this explorative review is to identify studies that can be used to support the development of a health economic model, and to estimate the model input parameters,

that will aim to answer the research questions of this assessment, but not to perform a systematic review.

5.2 Evaluation of costs, quality of life and cost-effectiveness

Subject to data availability, decision analytic modelling will be undertaken to determine the cost-effectiveness of AI-derived-software-assisted CT brain scan review, by a neuroradiologist or other healthcare professional, at the following decision points:

1) AI-derived-software-assisted review of non-enhanced CT brain scans compared with unassisted CT brain scan review, or AI-derived-software-assisted brain scan review using a different AI-derived technology, for guiding thrombolysis treatment decisions in people presenting or attending secondary care with a suspected acute stroke.

2a) AI-derived-software-assisted review of CT angiography brain scans compared with unassisted CT brain scan review, or AI-derived-software-assisted brain scan review using a different AI-derived technology, for guiding mechanical thrombectomy treatment decisions for people with an ischaemic stroke.

2b) AI-derived-software-assisted review of CT angiography and perfusion brain scans compared with unassisted CT angiography and perfusion brain scan review, or AI-derived-software-assisted brain scan review using a different AI-derived technology, for guiding mechanical thrombectomy treatment decisions in people with an ischaemic stroke, after a CT angiography brain scan.

Diagnosis and treatment strategies

The analysis will consider the diagnostic performance, and long-term consequences of the different AI-derived-software-assisted CT brain scan review technologies compared with unassisted CT brain scan review, and AI-derived-software-assisted brain scan review using a different AI-derived technology. For technologies for which the prognostic value is unclear, when feasible, assumptions will be made to provide some indication of the (range) of cost-effectiveness outcomes.

Model structure

A decision tree will capture diagnostic performance and other technology-related outcomes in the short term. This will feed into a health state transition model that will be used to capture long-term consequences.

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. Expected quality-adjusted life-years (QALYs) will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for the diagnostic technologies and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the technologies.

Issues relevant to analyses

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Deterministic sensitivity & scenario analyses will be performed, if necessary.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 01/11/2021. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	01/06/2021
Final protocol	25/06/2021
Final assessment report	16/12/2021
DAC 1	23/02/2022
DAC 2	26/04/2022

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Appendix 1: Example clinical effectiveness search strategy

Embase: 1974 to 22 June 2021
Searched: 23.6.21

1 exp brain ischemia/ (199252)
2 exp brain hemorrhage/ (150069)
3 basal ganglion hemorrhage/ (653)
4 cerebrovascular accident/ (226216)
5 brain infarction/ (55620)
6 blood vessel occlusion/ (11536)
7 (Stroke$ or apople$ or cerebral vasc$ or cerebrovasc$ or cerebro vasc$ or poststroke$ or encephalorrhag$ or hematencephalon$ or large vessel occlusion$).ti,ab,ot. (497902)
8 ((brain or blood flow) adj2 disturb$).ti,ab,ot. (2898)
9 ((sinus or sagittal) adj3 thromb$).ti,ab,ot. (7125)
10 (isch?emi$ adj3 (seizure$ or attack$ or thrombo$ or embolic or encephalopath$ or neural)).ti,ab,ot. (40451)
11 ((Bleed$ or h?emorrhag$) adj2 corpus callosum).ti,ab,ot. (27)
12 ((brain or cerebr$ or cerebell$ or cortical or Intraparenchymal or intracortical or vertebrobasil$ or hemispher$ or intracran$ or intra-cran$ or intracerebral or intratentorial or intra-tentorial or intraventricular or intra-ventricular or periventricular or peri-ventricular or supratentorial or supra-tentorial or anterior circulat$ or posterior circulat$ or basal gangli$ or global or focal or parenchymal or subarachnoid or sub-arachnoid or putaminal or putamen or posterior fossa or intra-axial or intraaxial or lacunar) adj3 (arrest$ or attack$ or isch?emi$ or infarct$ or insufficien$ or emboli$ or occlus$ or hypox$ or vasospasm or obstruction or vasculopath$ or failure$ or thromb$ or h?emorrhag$ or microh?emorrhag$ or accident$ or h?ematoma$ or bleed$ or microbleed$ or insult$)).ti,ab,ot. (292378)
13 (CVA or CVAS or MCA$ or ICH or ICHs or CVST or CVSTs or CVDST or CVT or CVDSTs or CVTs or LVO or LVOs).ti,ab. (81727)
14 or/1-13 (860679)
15 ((diagnos$ or predict$ or specificity or sensitiv$) adj4 (criteria or criterion or guideline$ or pattern$ or trend$ or utili$ or management or prevalence or initiat$ or distribution$ or coverage or variety or selection or spread or alternative$ or frequen$)).ti,ab,ot. (492536)
16 diagnosis/ or early diagnosis/ (1443415)
17 exp brain scintiscanning/ (9848)
18 Neurologic examination/ (70304)
19 Computer assisted tomography/ (776208)
20 Brain radiography/ (7761)
21 ((Brain or cerebral or neurologic$ or CT or head) adj2 (scan$ or scintigraph$ or examination$ or angiograph$ or image analys$ or perfusion$ or radiograph$)).ti,ab,ot,hw. (388322)
22 (CAT scan$ or CTA or CTP or neuroimag$ or neuro-imag$ or (comput$ adj2 tomograph$)).ti,ab,ot,hw. (1296975)
23 (Gamma encephalograph$ or Gammaencephalograph$ or Radio encephalograph$ or Radioencephalograph$).ti,ab,ot,hw. (48)
24 or/15-23 (3116480)
25 exp artificial intelligence/ (49304)

26 automated pattern recognition/ (16893)
27 decision support system/ (23870)
28 computer assisted diagnosis/ (40309)
29 Convolutional neural network/ (9654)
30 (Artificial intelligence or AI or machine intelligence or computer-aided triage$ or support vector machine$ or relevance vector machine$).ti,ab,ot. (74801)
31 ((automat$ or computer) adj2 (analys$ or diagnos$ or detect$)).ti,ab,ot. (54278)
32 ((deep or machine) adj learning).ti,ab,ot. (64740)
33 (decision support$ adj (software or tool$)).ti,ab,ot. (4642)
34 (CNN or CNNs or convNet or (convolut$ adj2 neural network$) or convolutional ANNs or convolutional ANN or convolutional NNs or convolutional NN).ti,ab. (15113)
35 automat$ hierarch$ evaluat$.ti,ab. (1)
36 (Aidoc or e-CTA or e-ASPECTS or e-stroke or brainomix or brainscan or "brainscan.ai" or icobrain or icometrix or qER or Qure or Zebra$ or e-CTP or briefcase or rapid CTA or rapid LVO or rapid core or rapid ASPECTS or rapid ICH or rapidai or blackford or "viz.ai" or viz or "ct perfusion 4d" or cercare or cina$ or Avicenna or accipio$ or maxQ AI or biomind or "biomind.ai" or ischemaview or rapid CTP or "qure.ai").ti,ab. (125441)
37 or/25-36 (393865)
38 14 and 24 and 37 (2051)
39 (letter or editorial or note).pt. (2733035)
40 38 not 39 (1988)
41 animal/ (1513528)
42 animal experiment/ (2691826)
43 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (7017023)
44 or/41-43 (7017023)
45 exp human/ (22447168)
46 human experiment/ (549694)
47 or/45-46 (22449055)
48 44 not (44 and 47) (5344219)
49 40 not 48 (1942)

Appendix 2: Related NICE guidance

Stroke and transient ischaemic attack in over 16s: diagnosis and initial management: Clinical guideline NG128 (2019) Available from: https://www.nice.org.uk/guidance/ng128 Date for review: not stated.

Alteplase for treating acute ischaemic stroke: Technology appraisal guidance TA264 (2012) Available from: https://www.nice.org.uk/guidance/ta264 Date for review: not stated.

Mechanical clot retrieval for treating acute ischaemic stroke: Interventional procedures guidance IPG548 (2016) Available from: https://www.nice.org.uk/guidance/ipg548 Date for review: not stated.