

National Institute for Health and Care Excellence

Draft for consultation

Stroke (update)

Evidence review C: TIA Imaging

NICE guideline

Intervention evidence review

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Draft for consultation

*This evidence review was developed by
the National Guideline Centre*

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1 Brain imaging after transient ischaemic attack (TIA)

1.1 Review question: After TIA, what is the optimal brain imaging strategy?

1.2 Introduction

The diagnosis of TIA is difficult, especially for non-specialist clinicians because the symptoms have, by definition, resolved, and there is no perfect diagnostic test. Making a diagnosis of a TIA is important because a) people with suspected TIA can have a range of other conditions (e.g. tumours or intracerebral haemorrhage, so called 'mimics') and b) people with confirmed TIA are at high risk of future ischemic stroke. The goal of assessment of suspected TIA is to establish the diagnosis and reduce the potential for future strokes by starting preventive treatments. Brain imaging might be helpful in excluding alternative diagnoses, improving risk prediction, or guiding treatment, but its role remains controversial. Previous NICE guidance and an HTA¹¹ advise that specialist assessment is necessary before making decisions regarding imaging in suspected TIA, and suggest that the role of MRI remains unproven. Variation across organisations suggests that previous recommendations have not been implemented appropriately and CT imaging is still being performed routinely (including prior to specialist assessment). Inappropriate radiation exposure from CT causes risk to the patient while the routine use of CT or MRI might be an inappropriate use of resources which offer no clinical benefit.

Computed tomography (CT) is insensitive to the small areas of acute ischaemia likely to underlie most TIA syndromes, while magnetic resonance imaging is very sensitive in detecting both acute ischaemia (in about 50% of patients) and haemorrhage of any age. Clinicians remain uncertain about the value of either CT or MRI in assessing suspected TIA. Since 2008 further evidence has emerged regarding the value of MRI in predicting the risk of future ischaemic events, including ischaemic strokes. The pattern of diffusion weighted imaging (DWI) lesions can also help in determining the likely mechanism of ischemic stroke or TIA. In light of these advances in knowledge about imaging technologies in TIA, an evidence review was required to investigate the best imaging strategy in patients presenting with suspected TIA.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 16 with suspected or confirmed TIA
Interventions	Magnetic resonance diffusion weighted imaging (MR DWI) MR DWI and computed tomography (CT) CT
Comparisons	Any combination of the above
Outcomes	<u>Critical</u> Stroke Mortality <u>Important</u> Modified Rankin scale (mRS)

	Quality of life Change in diagnosis or clinical management
Study design	Randomised controlled trials (diagnostic test and treat studies) Systematic reviews and meta-analyses of the above Prospective observational studies with a test and treat design if no RCTs are identified

1.4 1 **Methods and process**

2 This evidence review was developed using the methods and process described in
3 Developing NICE guidelines: the manual.⁹ Methods specific to this review question are
4 described in the review protocol in appendix A.

5 Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy
6 upto March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

1.5 7 **Clinical evidence**

1.5.1 8 **Included studies**

9 No relevant clinical studies comparing MR DWI and CT or any combination in a randomised
10 or observational test and treat study design were identified.

11 See also the study selection flow chart in appendix C.

12

1.5.2 3 **Excluded studies**

14 See the excluded studies list in appendix E.

15 An HTA¹¹ was identified that looked at whether MR with DWI is cost-effective in stroke
16 prevention compared with CT brain scanning in all patients with TIA or minor stroke. It is a
17 systematic review and meta-analysis of sensitivity/specificity of imaging strategies and also
18 looks at use of ABCD2 based scores. This was highlighted in the NICE surveillance report
19 and also as a key paper when discussing the protocol with the committee, however it did not
20 meet the protocol criteria for this question. The committee agreed that diagnostic accuracy
21 outcomes would not adequately answer the review question. The committee were particularly
22 interested in diagnostic test and treat outcomes. That is what happens downstream after
23 imaging in terms of observed stroke, mortality, functional outcome and changes decision
24 making and clinical management, to allow comparison of imaging strategies.

25

1.6 1 Economic evidence

1.6.1 2 Included studies

3 No relevant health economic studies were identified.

1.6.2 4 Excluded studies

5 One economic study relating to this review question was identified but was excluded due to
6 methodological limitations. ¹¹ This is listed in appendix E, with reasons for exclusion given.

7 See also study selection flowchart in appendix D.

1.6.3 8 Unit costs

9 **Table 2: UK costs of outpatient imaging**

Currency Description	Unit Cost
Magnetic Resonance Imaging of Head	
Magnetic Resonance Imaging Scan, One Area, without Contrast, 19 years and over	£139
Computed Tomography of Head	
Computerised Tomography Scan of One Area, without Contrast, 19 years and over	£86

10 *Source: NHS Reference Costs, 2016-2017*

1.7 11 Resource costs

12 The recommendation made by the committee based on this review (see section 1.9) that CT
13 imaging is not offered unless there is diagnostic doubt is likely to have a substantial impact
14 on resources to the NHS in England. The committee agreed this recommendation will
15 significantly reduce costs through greatly reducing the population requiring CT imaging in
16 emergency departments. Additional savings are likely to be made by improving the flow of
17 people with TIA to the TIA clinic and in the timeliness of delivering secondary prevention,
18 which reduces the risk of stroke. Further work is being carried out to quantify the potential
19 resource impact in this area.

20 The committee has also made a recommendation based on this review (see section 1.9) that
21 urgent MRI (including diffusion-weighted and blood sensitive sequences) to detect
22 ischaemia, haemorrhage or alternative pathologies should be 'considered' following expert
23 assessment in the TIA clinic. Unlike for stronger recommendations stating that interventions
24 should be adopted, it is not possible to make a judgement about the potential resource
25 impact to the NHS of recommendations regarding interventions that could be used, as
26 uptake is too difficult to predict. The committee was not confident of the effect of this
27 recommendation on MRI requests, acknowledging that this recommendation may slightly
28 increase the number of MRI requests compared to current practice. However, the committee
29 was confident that CT imaging will decrease and so expect that this will offset the potential
30 increase in MRI requests. The committee was uncertain whether overall these
31 recommendations will be cost saving.

32

33

1.8 1 Evidence statements

1.8.1 2 Clinical evidence statements

- 3 • No relevant published evidence was identified.

1.8.2 4 Health economic evidence statements

- 5 • No relevant economic evaluations were identified.

6

1.9 1 Recommendations

2 C1. Do not offer CT brain scanning to people with a suspected TIA unless there is clinical
3 suspicion of an alternative diagnosis that CT could detect for example, intracerebral
4 haemorrhage or mass lesion. [2019]

5 C2. Consider MRI (including diffusion-weighted and blood-sensitive sequences) to detect
6 ischaemia, haemorrhage or alternative pathologies after specialist assessment in the TIA
7 clinic. If imaging is done, perform it on the same day as the assessment. [2019]

1.9.1 8 Research Recommendation

9 RR1. Does early MRI brain scanning improve outcomes after suspected transient ischemic
10 attack (TIA)?

1.10 1 Rationale and impact

1.10.1 2 Why the committee made the recommendations

13 The committee agreed that CT is most useful when there is a clinical suspicion of finding a
14 CT-detectable lesion, such as intracerebral haemorrhage or mass lesion, and should not be
15 routinely performed for everyone with a suspected TIA. No evidence was identified from test-
16 and-treat trials. In these different imaging strategies are performed on randomised groups
17 followed by management on the basis of the results to compare patient outcomes of different
18 imaging strategies. In the committee's knowledge and experience, clinical assessment is the
19 best form of diagnosis at this point. Routine CT scanning of people with suspected TIA was
20 not thought to be good practice as it rarely confirms a diagnosis in these patients.

21 Routine CT imaging is common in current practice and the committee agreed that this could
22 waste resources, extend the length of stay in the emergency department, and expose people
23 to unnecessary radiation.

24 The committee discussed the possible risks of not offering CT brain imaging to everyone with
25 a suspected TIA. They agreed that, in the absence of clinical "red flag" indicators (for
26 example headache, anticoagulation, head injury, repetitive stereotyped events), it is rare for
27 a CT scan to reveal an alternative diagnosis needing a different referral pathway. Therefore
28 the numbers of referrals to TIA clinics should not increase greatly.

29 Clinical assessment by a specialist in a TIA clinic is important for identifying people who may
30 need MRI to detect ischaemia or alternative pathologies.

31 There was uncertainty about whether urgent, routine MRI screening improves the outcomes
32 for people with suspected TIA, and so the committee made a research recommendation in
33 this area.

1.10.2 4 Impact of the recommendations on practice

35 Not routinely offering CT brain imaging will be a change in practice for most providers
36 (especially in the emergency department), whereas MRI use in the TIA clinic aligns with
37 current practice.

38 The recommendations may have opposing impact implications. The committee was not
39 confident of the effect of this recommendation on MRI requests, acknowledging that this
40 recommendation may slightly increase the number of MRI requests. However, the committee
41 was confident that CT imaging will decrease and so expect that this will offset the potential
42 increase in MRI requests. The committee was therefore uncertain whether the

- 1 recommendations will be cost saving; it will be a tradeoff between a reduction of CT requests
- 2 against a potential increase of MRI requests.

1.11.3 The committee's discussion of the evidence

1.11.4 Interpreting the evidence

1.11.1.6 The outcomes that matter most

6 This review focused on the 'optimal' brain imaging strategy in terms of improvement in
7 patient outcomes. Critical outcomes for this review were stroke and mortality. Important
8 outcomes were identified as functional outcome (mRS), quality of life and change in
9 diagnosis or clinical management.

10 This review examined diagnostic test and treat outcomes, as the committee were particularly
11 interested in the downstream outcomes after imaging. This included stroke, mortality,
12 functional outcome and changes in decision making and clinical management. The
13 committee agreed that diagnostic accuracy outcomes were not the most important factor in
14 deciding on a strategy and therefore these would not provide as useful an insight for making
15 a practice recommendation.

16 No evidence was identified for this question.

1.11.1.7 The quality of the evidence

18 No relevant clinical studies comparing MR, DWI and CT alone or any combination in a test
19 and treat study design were identified. Therefore, there was no evidence to directly answer
20 the question of whether brain imaging (unenhanced CT or MRI) after suspected TIA affects
21 either subsequent treatment or early risk of stroke, or whether brain imaging of all suspected
22 TIA cases is appropriate or cost effective.

23 An HTA¹¹ was identified that looked at whether MR with DWI is cost-effective in stroke
24 prevention compared with CT brain scanning in all patients with TIA or minor stroke.
25 However, this was excluded because it did not meet the protocol for this question. This was
26 because:

- 27 • There were no studies that directly compared MR DWI with CT scanning
- 28 • the population included minor stroke as well as TIA
- 29 • no test-and-treat study designs were included.

1.11.1.8 Benefits and harms

31 In the absence of any evidence, the committee based discussions on clinical experience and
32 knowledge. The committee agreed that CT is most useful when there is a clinical suspicion of
33 finding a CT-detectable lesion, such as intracerebral haemorrhage or mass lesion, and
34 should not be applied routinely to all suspected TIA cases. If exclusion of intracerebral
35 bleeding is a clinical priority, for example, with those on anticoagulants or with a known
36 bleeding disorder, or other reasons to suspect intracerebral bleeding (subdural haematoma,
37 convexity subarachnoid haemorrhage, or intracerebral haemorrhage), then an unenhanced
38 CT head scan should be performed. The committee anticipates that in these cases, those
39 presenting to the ED would have the CT scan performed in ED, but those who present to
40 primary care should be urgently referred to secondary care where the scan would be done if
41 appropriate.

42 The committee discussed that routine CT imaging is common in current practice and could
43 waste resources, extend the length of stay in ED, and expose people to unnecessary
44 radiation. Therefore, they made a strong recommendation that CT brain scanning should not

1 be offered to people with a suspected TIA unless there is clinical suspicion of an alternative
2 diagnosis that CT could detect, for example, intracerebral haemorrhage or mass lesion.

3 The committee discussed the possible risks of not offering CT brain imaging to all people
4 with a suspected TIA. They agreed that, in the absence of specific clinical indicators (for
5 example, headache, anticoagulation) it is rare for a CT scan to reveal an alternative
6 diagnosis requiring a different referral pathway, and therefore the numbers of referrals to TIA
7 clinics should not increase greatly. The risk of missing a TIA diagnosis by not performing a
8 CT scan is also low because the committee agreed that the best diagnosis of TIA is by
9 clinical assessment.

10 Additionally, based on the opinion and experience of the committee, urgent MRI, within 24
11 hours, should be considered after expert assessment in the TIA clinic to detect the presence
12 and distribution of cerebral ischaemia, or alternative pathologies (TIA mimics, such as
13 tumours, demyelinating disorders or convexity subarachnoid haemorrhage). MRI may also
14 be needed to confirm the vascular territory of ischaemia before a decision is made to refer for
15 a carotid endarterectomy, and may suggest alternative stroke mechanisms, such as cardiac
16 embolism, large artery thrombo-embolism, haemodynamic compromise, or small vessel
17 occlusion. MRI can also improve the assessment of future risk of stroke. However, the
18 committee believed it was important to leave flexibility for clinicians in the TIA clinic to decide
19 on the need for brain imaging based on the clinical scenario and agreed that MRI will not be
20 required for all patients in a TIA clinic; therefore, the recommendation was to 'consider' MRI
21 to allow for clinical discretion on an individual case basis. The potential harms for MRI are
22 less than CT as there is no ionising radiation.

23 There was remaining uncertainty about whether urgent, routine MRI scanning versus
24 standard care improves the outcomes of suspected TIA patients and so a priority research
25 recommendation was framed in this area. The committee noted that this should be a cluster
26 randomised test-and-treat trial comparing urgent routine MRI to usual care for all cases of
27 suspected TIA within a TIA clinic.

1.1128 Cost effectiveness and resource use

29 No cost effectiveness evidence was included for the optimal brain imaging strategy after TIA
30 review. One health economic study was identified but was excluded due to methodological
31 limitations.

32 In the absence of economic evidence, the committee considered the unit costs of MR and CT
33 imaging. In the outpatient setting, non-contrast CT and MRI scans of one area currently cost
34 £86 and £139, respectively. The committee noted that the unit costs of the imaging strategies
35 are high and the population of those with suspected TIA is large. In addition, there is wide
36 variation in current practice and issues surrounding access to imaging, particularly MRI.

37 In current practice, CT imaging is widely used in the ED in patients with suspected TIA to rule
38 out other diagnoses, for example, intracerebral haemorrhage or a mass lesion. There is
39 usually limited access to MRI in the ED. As CT imaging only identifies persistent deficits,
40 people with TIA often have normal CT scans and are then sent to the TIA clinic where they
41 may receive further imaging, usually MRI. Currently people with suspected TIA can
42 experience delays in their transit through the ED, while awaiting CT imaging. The committee
43 agreed that when a diagnosis of TIA is confidently suspected, CT imaging should not be
44 routinely offered. The committee noted that CT imaging is only useful in specific cases when
45 there is a clinical suspicion of alternative diagnoses which may be detected by CT, for
46 example mass lesions or intracerebral haemorrhage.

47 The committee was confident this recommendation may significantly reduce costs through
48 greatly reducing the population requiring CT imaging in emergency departments, without
49 negatively affecting patient outcomes. Furthermore, the committee expects that, by not
50 routinely CT scanning patients with suspected TIA, there will be improvements in the flow of

1 people with suspected TIA to the TIA clinic and in the timeliness of delivering secondary
2 prevention, which is likely to improve patient outcomes and reduce downstream costs.

3 The committee agreed that the 'gold standard' diagnostic strategy for TIA is expert clinical
4 assessment. The committee agreed that MRI is much more sensitive to acute cerebral
5 ischaemia than CT imaging, with a sensitivity that decreases over time. MRI enables the
6 detection and localisation of ischaemia, which allows clarification of the stroke mechanism
7 and improved assessment of future risk. The committee agreed that the stroke
8 physician/neurologist in the TIA clinic should dictate the need for imaging, noting that MRI
9 will not be informative for all people with suspected TIA, such as those presenting late. The
10 committee was not confident of the effect of this recommendation on MRI requests,
11 acknowledging that this recommendation may slightly increase the number of MRI requests.
12 However, the committee was confident that CT imaging will decrease and so expect that this
13 will offset the potential increase in MRI requests. The committee was uncertain whether
14 overall these recommendations will be cost saving hence the research recommendation to
15 acquire better comparative data in this area

16 The committee noted that access to high quality MRI scanners is limited in some trusts and
17 in particular in smaller hospitals. This could impact the implementation of the
18 recommendation. The committee further discussed that undertaking an MRI scan takes more
19 time than a CT of the head without contrast, although newer MRI scanners are faster. The
20 number of MRI slots per day is currently limited, so there may be a need for dedicated MRI
21 slots for people with suspected TIA.

22 In conclusion, no cost effectiveness evidence was identified for the optimal brain imaging
23 strategy after TIA. The committee chose to recommend that CT scans are not offered to
24 those with suspected TIA, unless there is clinical suspicion of a CT detectable alternative
25 diagnosis. People with suspected TIA should undergo expert assessment, during which an
26 MRI scan may be considered. The committee thought that recommending against the use of
27 CT scans may offset any potential increase in costs due to the possible increase in use of
28 MRI scans. The committee chose to recommend that further research be done which
29 considers whether routine MRI screening for all those arriving in TIA clinics improves
30 outcomes.

1.1133 Other factors the committee took into account

32 The committee noted that imaging is performed routinely in some services, and sometimes
33 involves both CT and MRI. This suggests that current NICE recommendations in CG68 are
34 not being implemented appropriately.

35 The committee agreed that uncertainty about the need for brain scanning in this group
36 remains, with variations between clinics in protocols for scanning people with suspected TIA.
37 Often CT is used because of lack of access to MRI.

38 Regarding MRI, the committee acknowledged that timely access to MRI is not currently
39 standard in TIA clinics. Delayed access reduces the utility of MR-DWI for detecting transient
40 ischemic events as sensitivity reduces over time and, therefore, further reinforces the need
41 for early expert assessment and timely access to MRI.

42 The committee noted that brain imaging is often performed simultaneously with vascular
43 imaging of the intracerebral and extracranial arteries but did not assess this strategy as the
44 question addressed was about brain imaging only.
45

1 References

- 2 1. Coutts SB, Modi J, Patel SK, Aram H, Demchuk AM, Goyal M et al. What causes
3 disability after transient ischemic attack and minor stroke?: Results from the CT and
4 MRI in the Triage of TIA and minor Cerebrovascular Events to Identify High Risk
5 Patients (CATCH) Study. *Stroke*. 2012; 43(11):3018-22
- 6 2. Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD et al. CT/CT
7 angiography and MRI findings predict recurrent stroke after transient ischemic attack
8 and minor stroke: results of the prospective CATCH study. *Stroke*. 2012; 43(4):1013-
9 7
- 10 3. Coutts SB, O'Reilly C, Hill MD, Steffenhagen N, Poppe AY, Boyko MJ et al.
11 Computed tomography and computed tomography angiography findings predict
12 functional impairment in patients with minor stroke and transient ischaemic attack.
13 *International Journal of Stroke*. 2009; 4(6):448-53
- 14 4. Coutts SB, Simon JE, Eliasziw M, Sohn CH, Hill MD, Barber PA et al. Triaging
15 transient ischemic attack and minor stroke patients using acute magnetic resonance
16 imaging. *Annals of Neurology*. 2005; 57(6):848-54
- 17 5. Hefzy H, Neil E, Penstone P, Mahan M, Mitsias P, Silver B. The addition of MRI to CT
18 based stroke and TIA evaluation does not impact one year outcomes. *Open*
19 *Neurology Journal*. 2013; 7:17-22
- 20 6. Kleinman JT, Mlynash M, Zaharchuk G, Ogdie AA, Straka M, Lansberg MG et al.
21 Yield of CT perfusion for the evaluation of transient ischaemic attack. *International*
22 *Journal of Stroke*. 2015; 10(A100):25-9
- 23 7. Moreau F, Asdaghi N, Modi J, Goyal M, Coutts SB. Magnetic resonance imaging
24 versus computed tomography in transient ischemic attack and minor stroke: The
25 more you see the more you know. *Cerebrovascular Diseases Extra*. 2013; 3(1):130-6
- 26 8. Moreau F, Modi J, Almekhlafi M, Bal S, Goyal M, Hill MD et al. Early magnetic
27 resonance imaging in transient ischemic attack and minor stroke: do it or lose it.
28 *Stroke*. 2013; 44(3):671-4
- 29 9. National Institute for Health and Care Excellence. Developing NICE guidelines: the
30 manual. London. National Institute for Health and Care Excellence, 2014. Available
31 from:
32 <http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview>
- 33 10. Souillard-Scemama R, Tisserand M, Calvet D, Jumadilova D, Lion S, Turc G et al. An
34 update on brain imaging in transient ischemic attack. *Journal of Neuroradiology*.
35 2015; 42(1):3-11
- 36 11. Wardlaw J, Brazzelli M, Miranda H, Chappell F, McNamee P, Scotland G et al. An
37 assessment of the cost-effectiveness of magnetic resonance, including diffusion-
38 weighted imaging, in patients with transient ischaemic attack and minor stroke: a
39 systematic review, meta-analysis and economic evaluation. *Health Technology*
40 *Assessment*. 2014; 18(27)

41

1 Appendices

2 Appendix A: Review protocols

3 Table 3: Review protocol: TIA Imaging

Field	Content
Review question	After TIA, what is the optimal brain imaging strategy?
Type of review question	Diagnostic (diagnostic test and treat studies only) A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine whether MR DWI is effective in diagnosing TIA, compared with CT brain scanning, to guide secondary stroke prevention.
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with suspected or confirmed TIA
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Diagnsotic tests: <ul style="list-style-type: none"> • MR diffusion weighted imaging (MR DWI) • MR DWI and CT • CT Subsequent treatments for secondary stroke prevention if TIA is diagnosed include: <ul style="list-style-type: none"> • antiplatelet agents, • blood pressure management, • anticoagulation in selected patients e.g. people with AF, • exclusion of diabetes, • management of dyslipidaemia including statins, • diet and lifestyle advice, particularly smoking cessation.
Eligibility criteria – comparator(s) / control or reference (gold) standard	Diagnsotic tests: <ul style="list-style-type: none"> • MR diffusion weighted imaging (MR DWI) • MR DWI and CT • CT Subsequent treatments for secondary stroke prevention if TIA is diagnosed: <ul style="list-style-type: none"> • antiplatelet agents, • blood pressure management, • anticoagulation in selected patients e.g. people with AF, • exclusion of diabetes, • management of dyslipidaemia including statins, • diet and lifestyle advice, particularly smoking cessation.
Outcomes and prioritisation	Critical Stroke at 7 days, 90 days and 1 year Mortality at 7 days, 90 days and 1 year Important Modified Rankin Scale at 90 days and 1 year Quality of life at 90 days and 1 year

Field	Content
	Change in diagnosis or clinical management
Eligibility criteria – study design	Randomised controlled trials (diagnostic test and treat studies) Systematic reviews and meta-analyses of the above Prospective observational studies if no RCTs are identified
Other inclusion exclusion criteria	Inclusion Include studies on ‘minor stroke’ and downgrade for indirectness Language: Restrict to English only Settings: Hospital, Emergency department, Specialist stroke unit, Mobile units Exclusion Haemorrhagic stroke
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups to investigate if heterogeneity is present Time from symptom onset to imaging (<24hr/>24hr, <1 week/> 1 week) ABCD2 score
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	<ul style="list-style-type: none"> • EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • MS Excel will be used for data extraction and critical appraisal for health economic studies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Databases: Medline, Embase, Cochrane Library, CINAHL, Social Care Online, PsycINFO Language: Restrict to English only Date restriction: none Key papers: <ol style="list-style-type: none"> 1. Boulanger JM, Coutts SB, Eliasziw M et al. Diffusion-weighted imaging-negative patients with transient ischemic attack are at risk of recurrent transient events. <i>Stroke</i> 2007;38(8):2367–2369. 2. Prabhakaran S, Chong JY, Sacco RL. Impact of abnormal diffusion-weighted imaging results on short term outcome following transient ischemic attack. <i>Archives of Neurology</i> 2007;64(8):1105–1109. 3. Calvet D. Management and outcome of patients with transient ischemic attack admitted to a stroke unit. <i>Cerebrovascular Diseases</i> 2007;24(1):80–85. 4. Coutts SB, Simon JE, Eliasziw M et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. <i>Annals of Neurology</i> 2005;57(6):848–854. 5. Purroy F, Montaner J, Rovira A et al. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. <i>Stroke</i> 2004;35(10):2313–2319.

Field	Content
	<p>6. Brazzelli M, Sandercock PA, Chappell FM et al. (2009) Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. [Review] [155 refs]. Cochrane Database of Systematic Reviews CD007424.</p> <p>7. Wardlaw J, Brazzelli M, Miranda H et al. (20-6-2014) An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. Health Technology Assessment (Winchester, England) 18:1-368.</p>
Identify if an update	<p>No (recommendation made in CG68, but no specific review). 5 studies were included in the original guideline in explanatory text, but not reviewed.</p> <p>Recommendations from CG68</p> <p>1.2.1.2 People who have had a suspected TIA who are at high risk of stroke (for example, an ABCD2 score of 4 or above, or with crescendo TIA) in whom the vascular territory or pathology is uncertain should undergo urgent brain imaging (preferably diffusion-weighted MRI [magnetic resonance imaging]).</p> <p>1.2.1.3 People who have had a suspected TIA who are at lower risk of stroke (for example, an ABCD2 score of less than 4) in whom the vascular territory or pathology is uncertain should undergo brain imaging (preferably diffusion-weighted MRI).</p> <p>1.2.2.1 People who have had a suspected TIA who need brain imaging (that is, those in whom vascular territory or pathology is uncertain) should undergo diffusion-weighted MRI except where contraindicated, in which case CT (computed tomography) scanning should be used.</p>
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	<p>Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual</p> <p>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/</p>
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment –	For details please see section 6.2 of Developing NICE guidelines: the

Field	Content
publication bias, selective reporting bias	manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

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2 **Table 4: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their</p>

relevance to the questions covered in this update and whether more applicable evidence is also identified.

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).⁹

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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2 **Appendix B: Literature search strategies**

3 The literature searches for this review are detailed below and complied with the methodology
4 outlined in Developing NICE guidelines: the manual 2014, updated 2017

5 [https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-](https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869)
6 pdf-72286708700869

7 *For more detailed information, please see the Methodology Review.*

8 **B.1.8 Clinical search literature search strategy**

9 Searches were constructed using a PICO framework where population (P) terms were
10 combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are
11 rarely used in search strategies for interventions as these concepts may not be well
12 described in title, abstract or indexes and therefore difficult to retrieve. Search filters were
13 applied to the search where appropriate.

14 **Table 5: Database date parameters and filters used**

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 19 February 2018	Exclusions Randomised controlled trials Systematic review studies Diagnostic tests studies
Embase (OVID)	1974 – 19 February 2018	Exclusions Randomised controlled trials Systematic review studies Diagnostic tests studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 2 of 12 CENTRAL to 2018 Issue 1 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

15 **Medline (Ovid) search terms**

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	exp Brain Ischemia/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	Ischemic Attack, Transient/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/

10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	exp tomography/
31.	tomograph*.ti,ab.
32.	(NCCT or CT or UHCT).ti,ab.
33.	((CAT or body) adj2 scan*).ti,ab.
34.	or/30-33
35.	Magnetic Resonance Imaging/
36.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
37.	(MRI or NMR or NMRI or fMRI or MR or DWI).ti,ab.
38.	Diffusion Magnetic Resonance Imaging/
39.	((diffusion-weighted or T2-weighted) adj2 imag*).ti,ab.
40.	or/35-39
41.	29 and 34 and 40
42.	Meta-Analysis/
43.	Meta-Analysis as Topic/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.

52.	or/42-51
53.	randomized controlled trial.pt.
54.	controlled clinical trial.pt.
55.	randomi#ed.ab.
56.	placebo.ab.
57.	randomly.ab.
58.	clinical trials as topic.sh.
59.	trial.ti.
60.	or/53-59
61.	exp "sensitivity and specificity"/
62.	(sensitivity or specificity).ti,ab.
63.	((pre test or pretest or post test) adj probability).ti,ab.
64.	(predictive value* or PPV or NPV).ti,ab.
65.	likelihood ratio*.ti,ab.
66.	likelihood function/
67.	((area under adj4 curve) or AUC).ti,ab.
68.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
69.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
70.	gold standard.ab.
71.	or/61-70
72.	41 and (52 or 60 or 71)
73.	93 or 72

1 Embase (Ovid) search terms

1.	((mini or minor or mild or acute) adj2 (stroke or strokes)).ti,ab.
2.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
4.	*Transient ischemic attack/
5.	(isch?emi* adj2 attack*).ti,ab.
6.	TIA*.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/

20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
27.	25 not 26
28.	exp x-ray computed tomography/
29.	tomograph*.ti,ab.
30.	(NCCT or CT or UHCT).ti,ab.
31.	((CAT or body) adj2 scan*).ti,ab.
32.	or/28-31
33.	nuclear magnetic resonance imaging/
34.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
35.	(MRI or NMR or NMRI or fMRI or MR or DWI).ti,ab.
36.	diffusion weighted imaging/
37.	((diffusion-weighted or T2-weighted) adj2 imag*).ti,ab.
38.	or/33-37
39.	27 and 32 and 38
40.	systematic review/
41.	Meta-Analysis/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	random*.ti,ab.
52.	factorial*.ti,ab.
53.	(crossover* or cross over*).ti,ab.
54.	((doubl* or singl*) adj blind*).ti,ab.
55.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
56.	crossover procedure/
57.	single blind procedure/
58.	randomized controlled trial/
59.	double blind procedure/
60.	or/51-59
61.	exp "sensitivity and specificity"/
62.	(sensitivity or specificity).ti,ab.

63.	((pre test or pretest or post test) adj probability).ti,ab.
64.	(predictive value* or PPV or NPV).ti,ab.
65.	likelihood ratio*.ti,ab.
66.	((area under adj4 curve) or AUC).ti,ab.
67.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
68.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
69.	diagnostic accuracy/
70.	diagnostic test accuracy study/
71.	gold standard.ab.
72.	or/61-71
73.	39 and (50 or 60 or 72)

1 Cochrane Library (Wiley) search terms

#1.	(mini or minor or mild or acute) near/2 (stroke or strokes):ti,ab
#2.	MeSH descriptor: [Brain Ischemia] explode all trees
#3.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#4.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#5.	(isch?emi* near/2 attack*):ti,ab
#6.	TIA*:ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#9.	tomograph*:ti,ab
#10.	(NCCT or CT or UHCT):ti,ab
#11.	((CAT or body) near/2 scan*):ti,ab
#12.	(or #8-#11)
#13.	MeSH descriptor: [Magnetic Resonance Imaging] this term only
#14.	((magnetic or nuclear) near/2 resonance near/3 imag*):ti,ab
#15.	(MRI or NMR or NMRI or fMRI or MR or DWI):ti,ab
#16.	MeSH descriptor: [Diffusion Magnetic Resonance Imaging] this term only
#17.	((diffusion-weighted or T2-weighted) near/2 imag*):ti,ab
#18.	(or #13-#17)
#19.	#7 and #12 and #18

B.2.2 Health Economics literature search strategy

3 Health economic evidence was identified by conducting a broad search relating to the stroke
4 population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated
5 after March 2015) and the Health Technology Assessment database (HTA) with no date
6 restrictions. NHS EED and HTA databases are hosted by the Centre for Research and
7 Dissemination (CRD). Additional searches were run on Medline and Embase for health
8 economics studies.

9

1 **Table 6: Database parameters and filters used**

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 – March 2015	None

2 **Medline (Ovid) search terms**

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.

27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/
40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/
46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

1 Embase (Ovid) search terms

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/

10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

47.	(finance* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

1 NHS EED and HTA (CRD) search terms

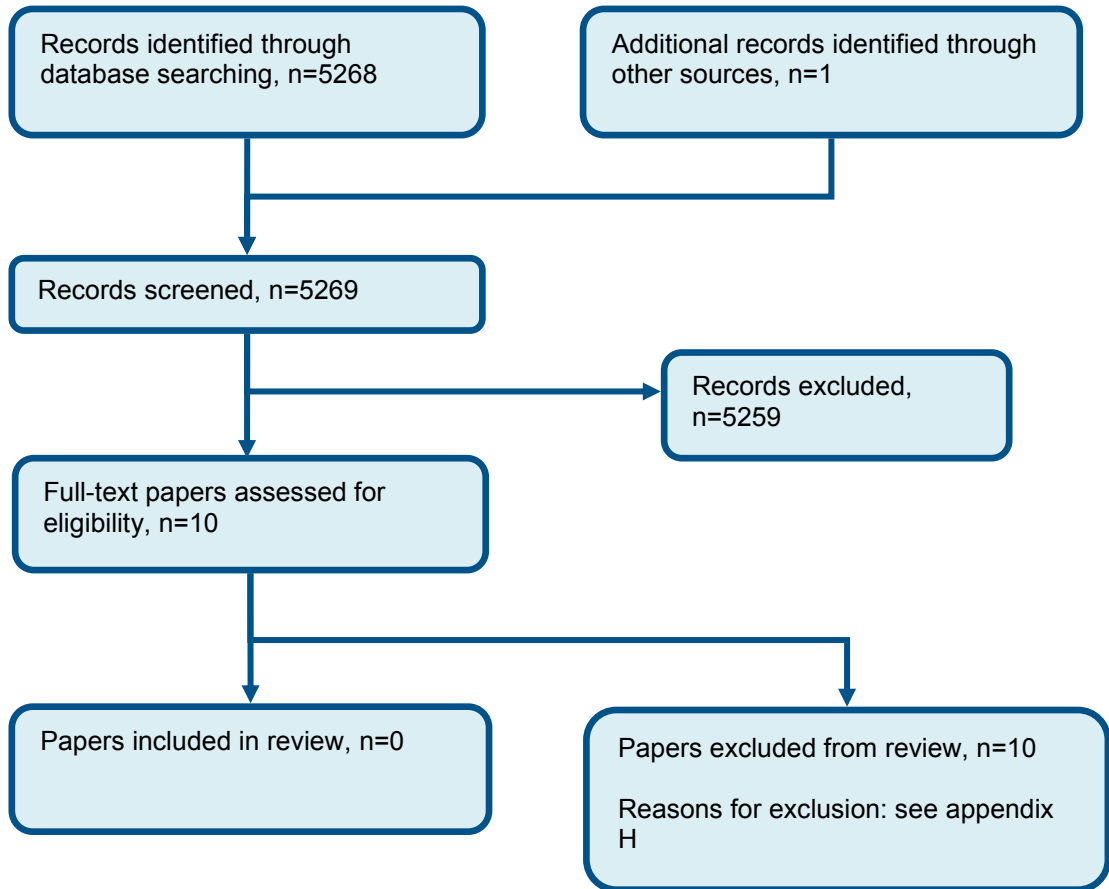
#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy))
#4.	((CVA or poststroke or poststrokes))
#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*))
#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

2

3

1 Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of brain imaging in TIA

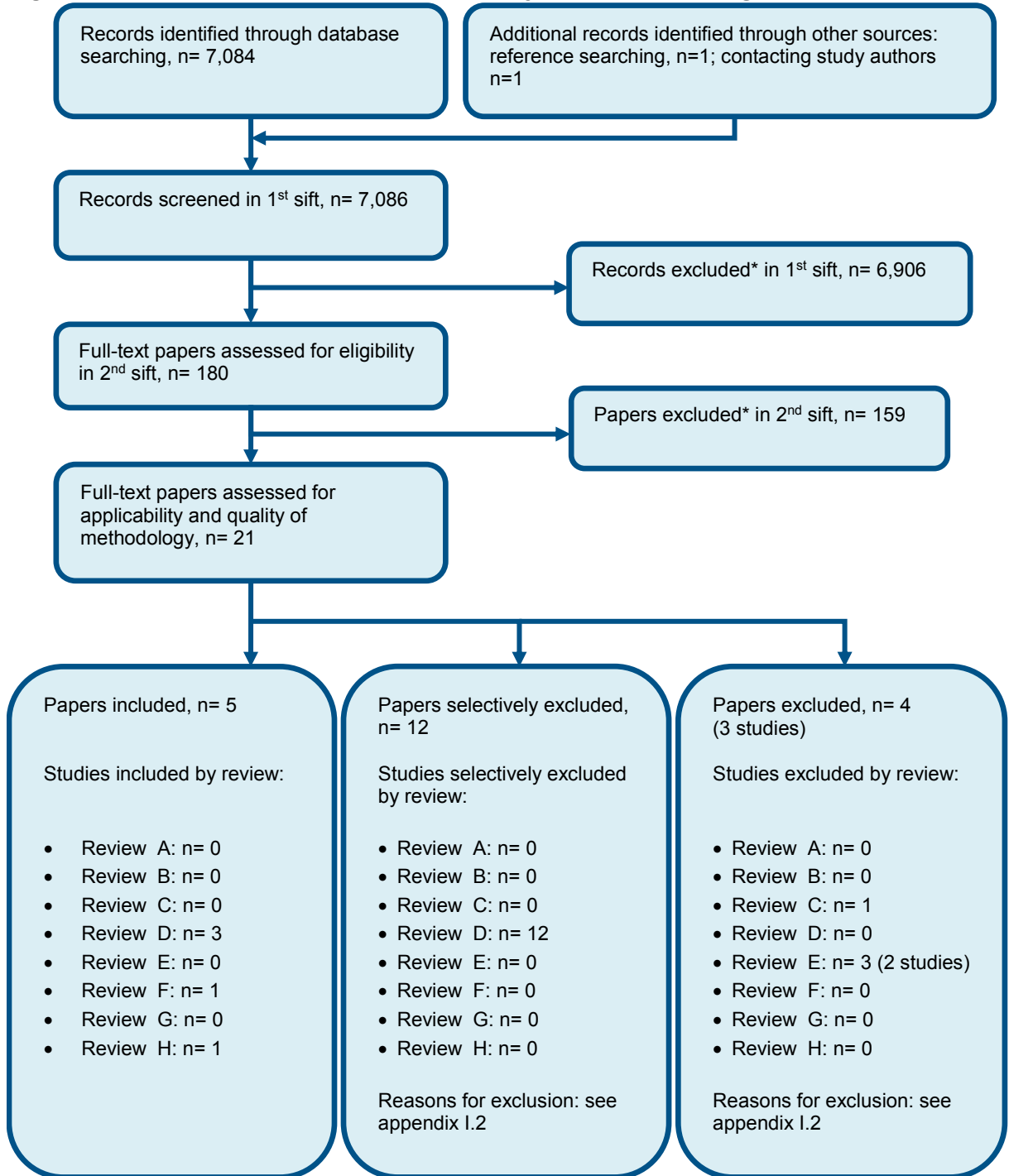


2

3

1 Appendix D: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

1 Appendix E: Excluded studies

E.1.2 Excluded clinical studies

3 Table 7: Studies excluded from the clinical review

Coutts, 2012 ¹	Incorrect study type; no direct comparison
Coutts, 2012 ²	Incorrect study type
Coutts, 2009 ³	Incorrect study type; no direct comparison
Coutts, 2005 ⁴	Incorrect study type; no direct comparison
Hefzy, 2013 ⁵	Incorrect population
Kleinman, 2015 ⁶	Incorrect intervention
Moreau, 2013 ⁷	Incorrect study type
Moreau, 2013 ⁸	Incorrect intervention
Souillard-Scemama, 2015 ¹⁰	Incorrect study type; non systematic review
Wardlaw 2014 ¹¹	Incorrect study type

4

E.2.5 Excluded health economic studies

6 Table 8: Studies excluded from the health economic review

Reference	Reason for exclusion
Wardlaw 2014 ¹¹	This study was assessed as directly applicable with very serious limitations and so was excluded from the health economic review.

7

8

1 Appendix F: Research recommendation

F.1.2 Does early MRI brain scanning improve outcomes after suspected transient ischemic attack (TIA)?

4 Why this is important:

5 Stroke is the single largest cause of adult disability and the third most common cause of
 6 death in the UK. People with TIA are at higher risk for a subsequent stroke. The diagnosis of
 7 TIA is made by specialist assessment and remains a clinical diagnosis based primarily on the
 8 clinical history of the TIA event. Secondary prevention strategies are based on this
 9 assessment and are vital to reduce the risk of future stroke. It is not known whether
 10 information provided by an early MRI brain scan – within 24-48 hours of the TIA event –
 11 improves on the clinical assessment, secondary prevention strategies or overall outcomes
 12 after TIA.

13 Criteria for selecting high-priority research recommendations:

PICO question	<p>Population: People aged over 16 years of age with suspected transient ischemic attack (TIA)</p> <p>Intervention(s): Routine MRI for all patients within 24-48 hours of TIA event.</p> <p>Comparison: Standard care based on clinical judgement and local protocols (i.e. no brain imaging, MRI at various time points or CT brain imaging if there is diagnostic doubt).</p> <p>Outcome(s): Stroke following TIA, mortality, recurrent vascular events, certainty of diagnosis, change in clinical management as a result of the MRI, improved elucidation of TIA mechanism, brain complications (bleeds), radiation exposure (from reduction in use of CT scans), quality of life</p>
Importance to patients or the population	<p>People who have a TIA are a high risk group for future disabling stroke. If doing an MRI in all those with a suspected TIA had a favourable impact on the risk of stroke then there would be a positive impact with fewer people left disabled, and with impaired quality of life. If doing an MRI improved the understanding of the underlying cause of a TIA (for example by paroxysmal atrial fibrillation [PAF], cerebral amyloid angiopathy [CAA]) this would improve secondary prevention strategies and lead to fewer incident strokes. There may also be reduced radiation exposure as a consequence of fewer CT head scans required.</p>
Relevance to NICE guidance	<p>Currently there is a lack of evidence of the benefits of brain imaging with MRI following TIA. An answer to this question would mean access to a more robust evidence base and would enable an analysis of cost effectiveness. A future NICE committee could then answer the question – should everyone with a suspected TIA have an MRI brain scan within 24 hours of the event?</p>
Relevance to the NHS	<p>The type and extent of brain imaging for people with suspected TIA is highly variable within the NHS. Some suspected TIA patients have no brain imaging, some have CT brain scans and others MRI at variable time points following the TIA. New NICE guidance on this issue would really help stroke services and imaging departments plan for future brain imaging requirements for people with suspected TIA. If there was good evidence for MRI brain imaging after TIA then this would have an impact on service delivery within radiology departments. It may lead to far fewer CT head scans being performed in this cohort. If routine MRI for all patients reduces the number of recurrent vascular events, then the upfront costs of imaging may be recuperated through a reduction in downstream costs such as rehabilitation and long term care. This could result in cost savings for the NHS.</p>

National priorities	There will be a new 'stroke strategic plan' launched in 2018/19 by The Stroke Association and NHS England. TIA and stroke will be covered in this document and responsive services for people with suspected TIA will be a priority area.
Current evidence base	The evidence review in the clinical guideline found no test-and-treat trials directly comparing CT brain imaging with MR imaging after TIA and there was a lack of a good comprehensive evidence base for MR imaging after TIA. There was also a lack of studies on cost effectiveness of brain imaging after suspected TIA.
Equality	Not relevant to this question. All groups would be considered in the research.
Study design	The most appropriate design would be a cluster (wedge) randomised test-and-treat trial design where people with suspected TIA are randomised in specific clusters to MRI at different early time points following the initial event or to standard care. Within a proposed intervention group (i.e. those having MRI) there would be a treatment algorithm for participating clinicians depending on the MRI findings. Treatment decisions and outcomes could then be analysed in the MRI and standard care (no MRI) clusters.
Feasibility	Most stroke services have daily TIA clinics seeing 900 or more suspected TIAs per year. The cost of an additional MRI scan is about £250. Service support costs should be low as there are daily clinics in most services from which the study could be run. Access of additional cases to MRI scanners will be the main issue for participating centres. As the stroke clinical research network is already established it is likely many centres would want to participate in such a study and utilise their research nurses to help recruitment.
Other comments	A potential funder would be the NIHR and/or The Stroke Association/British Heart Foundation (BHF). Similar studies have been performed within the field of cardiology (for example in the use of coronary CTA). There have been no previous funding attempts for this research question as far as the authors know.
Importance	<ul style="list-style-type: none"> High: the research is essential to inform future updates of key recommendations in the guideline.

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