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Project Description

1. Title
An assessment of the cost-effectiveness of magnetic resonance including diffusion weighted brain imaging in patients with transient ischaemic attack and minor stroke

2. Funding body
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4. Research Objectives
Our primary research objective is to determine whether magnetic resonance (MR) including diffusion-weighted imaging (DWI) as well as other relevant structural and blood-sensitive sequences is cost-effective in the majority of patients with transient ischaemic attack (TIA) or minor stroke to guide diagnosis and secondary stroke prevention, compared with the current alternative of Computerized tomography (CT) brain scanning.
Secondly to determine the cost and cost-effectiveness of increased use of MR including DWI and blood-sensitive sequences in patients presenting more than five days after TIA/minor stroke when CT will not be able to identify haemorrhage as the cause of stroke reliably.
Thirdly to estimate if ‘one stop’ brain and carotid imaging is more cost-effective than individual separate brain and carotid examinations, in what proportion of patients a ‘one stop’ approach could be used, and the practical and cost implications. Fourth, to determine physicians and radiologists current attitudes to increased use of MR in TIA/minor stroke, the availability, barriers to greater use, costs of increasing

availability and net effect on other patient groups in whom MR is commonly used. We will do this by modelling the effectiveness, cost-effectiveness and practical implications of using MR imaging in different proportions of patients with TIA or minor stroke at different times after symptom onset, using systematic reviews of the relevant literature, surveys of current practice and costs, existing stroke registry and cohort data and data linkage. If MR cannot be justified in all patients, then we will also determine in which subgroups of patients the use of MR is cost-effective. We will provide a range of options reflecting effect of using MR in different proportions of TIA/minor stroke patients to guide decision-making by health service purchasers.

5. Background

Stroke remains a major public health burden: In the UK, about 150,000 people have a stroke each year. About 30% die within six months and another 30% survive dependent on others for everyday activities, making stroke the commonest cause of dependency in adults and the third commonest cause of death in the world.[1] Stroke costs the NHS in England around £7bn per year.[2] Eighty percent of strokes are ischaemic and most ischaemic strokes are due to an artery in the brain becoming blocked by atherothromboembolism. Treatment of stroke is limited, so prevention is vital. About 20-40% of people have a warning TIA or minor non-disabling ischaemic stroke shortly before they have a major disabling stroke.[3;4] If these people can be assessed quickly, potential stroke causes identified and given the appropriate treatment, then many of these disabling strokes can be prevented.[5]

TIA is defined as 'a sudden loss of focal cerebral or monocular function lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, thrombosis or embolism associated with disease of the arteries, heart or blood'.[6] While the definition of TIA purely on the basis of clinical grounds is the subject of debate,[7;8] for the present time we will use this clinical definition. Patients with minor stroke, which only differs from TIA by symptoms or signs lasting more than 24 hours, are also at high risk of early recurrent stroke and need the same assessment and treatment as for patients with TIA to prevent a further disabling stroke or death. A small proportion of TIA/minor stroke (less than 5%) are actually due to a small haemorrhage in the brain, but this can only be distinguished by brain scanning.

TIA and minor stroke are common: In the UK, there are estimated to be 80,000 to 90,000 TIAs and minor strokes per year.[9] Therefore, the average regional hospital serving a population of 750,000 will see about 1000 suspected cases per year, i.e. 20 per week. Delivering effective stroke prevention to this number of people is challenging and requires highly organised stroke services that are able to respond rapidly and precisely. However the personal, societal, public health and financial burden of stroke in the UK is such that every effort should be made to limit the damaging effects of having a major disabling stroke, and to determine how to make best use of our available resources.[10-13]

TIA and minor stroke is a medical emergency: The period of highest risk of disabling stroke is in the first few hours and days after a TIA/minor stroke, thus making suspected TIA/minor stroke a medical emergency:[4;6;14;15] between 8% and 11.5% of patients will have a recurrent stroke by one week and between 11.5% and 15% by one month after TIA/minor stroke unless effective secondary prevention is started.[9] In the USA, there are about 240,000 TIAs per annum, of whom 25% had had a further TIA, a stroke or died by three months.[16] Prevention of recurrent stroke is by rapid identification of underlying risk factors (such as ipsilateral tight carotid artery stenosis, atrial fibrillation, hypercholesterolaemia, hypertension) and implementation of optimal medical (antiplatelet agents, statins, antihypertensives or anticoagulants where necessary)[5;6;17] and surgical treatment (endarterectomy for symptomatic moderate to severe carotid stenosis).[18]

Appropriate treatment of those whose symptoms are not due to vascular disease: The diagnosis of TIA/minor stroke brings a threat of disabling stroke or death and causes much worry for patients. Patients with definite acute ischaemic cerebrovascular disease are now given standard quadruple preventive therapy (antiplatelet, statin, angiotensin converting enzyme inhibitor and diuretic). In the light of the EXPRESS study, many patients with suspected acute ischaemic cerebrovascular disease following presentation with TIA/minor stroke are started on quadruple therapy pending specialist investigation and treatment. It is therefore important to ensure that the patients, whose symptoms after due investigation are proven not to be due to acute ischaemic cerebrovascular disease, particularly the small proportion (<5%) whose symptoms are due to a small haemorrhage, then avoid inappropriate or unnecessary and possibly hazardous drug treatment. So, if MR imaging can reliably help exclude acute ischaemic cerebrovascular disease as the cause of symptoms, then an additional benefit is that patients will avoid the inconvenience and risk (of adverse drug reactions) and the health service will avoid the cost of unnecessary drug treatment.

Clinical stroke risk prediction: Several scoring systems have been devised that aim to improve identification of patients at high risk of disabling recurrent stroke after TIA/minor stroke: a score developed in 469 patients with TIA seen in the 1980's based on clinical variables;[19] a score developed in the European Carotid Surgery Trial (1980's to mid 1990's) data;[20] the ABCD score developed using data from a population-based stroke and TIA registry conducted in the 1980's (Oxfordshire Community Stroke Project – OCSP) and tested in a repeat study in the same population in the early 2000's (Oxford Vascular Study – OxVasc);[21] an updated version of this derived in the OCSP TIA patients and patients attending a private health provider in the USA and tested in OxVasc and more USA patients, the ABCD2 score;[22] the Essen Stroke Risk Score which was derived from a subset of ischaemic stroke patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial and validated in two observational studies and in data from another stroke prevention trial;[23] the Stroke Prognosis Instruments I and II (SPI-I and SPI-II) were developed in medical stroke prevention trials and validated in three independent cohorts;[24] and the Life Long after Cerebral Ischaemia score (LiLAC), which was based on data from the Dutch TIA trial (1986-1989), has not been externally validated.[25] All except two[20;24] of these scores use only simple clinical features so are rapid and easy to apply without needing complex technologies.[19;21;22;25] For example, the ABCD2 score uses age, blood pressure, clinical features, duration of symptoms and diabetes to derive a score from zero to seven. These scores could help to reduce delays to reaching medical attention and to triage patients,[26] so that those needing most rapid treatment such as carotid endarterectomy would reach surgery more quickly. They might also improve the accuracy of clinical diagnosis of TIA by non-stroke physicians, thereby also making better use of resources.

Problems with clinical stroke risk prediction: Many of these scores performed well in the population from which they were derived and often also in initial testing in a different cohort,[27;28] but then wider use uncovered difficulties. For example, independent testing of the ABCD and ABCD2 scores[22] has not been universally positive.[29;30] While in the OxVasc Study, the ABCD2 score was highly predictive of recurrent stroke within seven days of TIA ($p<0.01$), it did not predict stroke between eight and 90 days, because in this group, patients with lower scores had a higher risk of stroke than those with high ABCD2 scores ($p=0.04$).[30] The ABCD2 score also did not predict recurrent stroke in patients with minor stroke (as opposed to TIA). Thus TIA clinical risk prediction scores may not usefully predict stroke risk more than seven days after TIA and may be of limited value in patients with minor stroke. Most scores were devised and tested in highly selected populations of patients with definite TIA/minor stroke such as randomised multicentre trials or observational

studies where the patient had to have a definite TIA/minor stroke to get into the study. However this is not the population of *suspected* TIA/minor stroke that typically presents to the 'front door' of the hospital. In this *unselected* population, up to 50% do not ultimately turn out to have had a TIA/minor stroke and therefore should have a low risk of recurrent stroke.[31] However the net effect of applying a clinical risk score in this mixed population was that many *true* TIA/minor strokes were given a low ABCD2 score and therefore would have missed rapid access to stroke services.[31] In this sense, the use of a clinical risk score could have actually led to a *net failure* to prevent recurrent stroke. This reflects a general limitation of low specificity scoring or screening systems - namely that while they may detect the small proportion of patients with particularly high risk of recurrent stroke, many recurrent strokes actually occur in patients deemed to be at moderate or low risk only (because there are many more of them). Widespread use of clinical risk scores in this setting could therefore put at risk patients in a 'slow stream' who would then potentially not receive treatment quickly enough to prevent stroke.

Could stroke prediction scores be improved with imaging?: Part of the problem may be that a) the clinical diagnosis of TIA/minor stroke is difficult and b) the clinical findings have low specificity for the likely underlying cause, but the future stroke risk is closely related to the cause. The clinical diagnosis of TIA and minor stroke is made difficult, especially for non-experts, by the high proportion of patients (up to 50%)[11;31-34] that actually have common mimics of TIA/minor stroke. Common mimics include migraine, transient global amnesia, epilepsy, simple faints, tumours, functional disorders, etc.[31;33] It is not possible to determine the cerebral pathological cause of symptoms, i.e. whether infarct, haemorrhage or mimic (e.g. tumour), without a brain scan.[35;36] The conventional brain scanning technique for stroke and TIA is CT, now widely available in the NHS. While CT excludes tumours and haemorrhage if done acutely,[37] it is insensitive to small infarcts, so does not 'positively' diagnose TIA/minor stroke.[38] CT demonstrates an infarct in a maximum of 50% of minor acute strokes[39] and 43% of mixed minor stroke and TIA,[40] although the sensitivity may be lower in older patients with brain tissue loss and leukoaraiosis. Nonetheless, the presence of an infarct on CT in patients presenting with TIA is associated with increased short term risk of stroke,[41] CT has high specificity for ischaemia,[42] visible infarction on CT is an independent predictor of poor outcome (dependency or death) after any ischaemic stroke,[39;43] CT is very accurate for haemorrhage within the first five days of symptoms[38;42] and for tumours and other non-vascular causes of sudden neurological symptoms, giving it many advantages to balance its two disadvantages - the low sensitivity for acute ischaemic stroke and for small haemorrhages that are more than five days old.

Some have questioned the usefulness of scores that do not incorporate significant carotid disease or other potential cardioembolic sources.[44] However, only two scoring systems included carotid stenosis as part of the risk prediction,[20;24] and found, along with other studies,[45] that adding tight carotid stenosis did improve risk prediction. Carotid imaging is an integral part of the assessment of TIA and minor stroke. Its cost-effectiveness was assessed in a previous HTA-funded project by our group.[11] This work showed that rapid access to carotid imaging to identify and measure carotid stenosis was the most cost-effective way of using carotid imaging, and that the four non-invasive imaging methods functioned similarly in terms of stroke prevention, although ultrasound was the most cost-effective of the four techniques if used early after TIA/minor stroke.[46] The focus of the present application is on how to improve stroke prevention through use of brain imaging techniques, so comparative carotid imaging will not be considered further.

The alternative brain imaging test – advantages of MR: a) ***Higher sensitivity for ischaemic lesions.*** MR imaging, if it includes DWI, is very sensitive to ischaemia. MR imaging is widely used to investigate many neurological disorders, musculoskeletal problems and in oncology. MR imaging is very versatile because

different sequences can be used to highlight different types of pathology relevant to stroke. For example, DWI is very sensitive to changes in the mobility of water in the brain; one of the earliest changes in the brain at the onset of ischaemia is cell swelling which reduces the extracellular space and hence restricts water movement. Thus, early ischaemia shows up well on DWI, even very early after the symptoms start and even in very small lesions causing mild symptoms.[47] DWI primarily displays ischaemic areas as white on a dark background, so ischaemic lesions are much more obvious than they are on CT scanning, where ischaemic lesions appear as dark on a dark background. MR DWI shows even very tiny ischaemic lesions soon after symptom onset in 16% to 67% of TIAs (mean 37%)[48;49] and about 70% to 90% of minor strokes overall, even weeks after the event.[42;47;49-52] Currently, with CT scanning, if the scan provides no positive evidence of an ischaemic lesion, the diagnosis of ischaemia is often assumed if the scan has excluded haemorrhage and stroke mimics. By contrast, MR including DWI could help make a 'positive' diagnosis of brain ischaemia in TIA/minor stroke in a larger proportion of (but not all) patients.

b) ***Higher sensitivity for haemorrhage in patients presenting late.*** MR, if it includes T2*-weighted imaging (also known as Gradient Echo) or equivalent, is very sensitive to haemorrhage, even years after the event. CT is very sensitive to acute haemorrhage but cannot reliably detect haemorrhage in patients who first present more than five days after a minor ischaemic stroke. The high sensitivity of MR T2* sequences for haemorrhage is clinically very helpful in such patients – and can avoid inappropriate use of antiplatelet agents, anticoagulants and carotid endarterectomy in patients with haemorrhagic stroke.

c) ***Defining the arterial territory(ies) affected***. MR can also help management in other ways. In some patients with carotid stenosis it is difficult to decide if the clinical event occurred in the territory of that artery if not.[53] DWI is helpful, if it can confirm that a TIA/minor ischaemic stroke was in the territory of a tight carotid stenosis, so leading to endarterectomy.[53] The presence of lesions in several territories would indicate a need to search a more proximal source of embolism, e.g. in the heart.[54]

d) ***Excluding acute ischaemic cerebrovascular disease as the cause.*** If MR is proven also to have both high specificity, it will, by helping to exclude acute ischaemic cerebrovascular disease as the cause of symptoms and if in a large enough proportion of patients, potentially have a greater role in avoiding unnecessary or inappropriate treatment.

The evidence on the contribution of MR to diagnosis, stroke prediction and hence potential for patient management and cost-effectiveness after TIA/minor stroke is conflicting. No studies have addressed the cost-effectiveness of using MR including DWI and other relevant sequences in TIA/minor stroke. Most studies of cost-effectiveness of imaging in stroke have either concentrated on hyperacute disabling stroke[35;55] or on carotid imaging for carotid stenosis[11] as part of carotid endarterectomy.[56] There are no clinical trials of diagnostic accuracy or effect on prediction of prognosis of MR including DWI and other relevant sequences, only smallish observational studies, from which it is unclear whether DWI adds prognostic information to simple clinical scoring systems. The 29 studies of MR DWI in patients with TIA or TIA and minor stroke published since 1999 include 2881 patients imaged between a few hours of onset of symptoms and nearly three weeks after the event. DWI was positive for ischaemic change in 37% (mean, ± 12% SD, range 16-67%).[48;49;57-59] Note: some studies are by the same research groups (so there may be some data duplication): all are single centre studies (so lack generalisability); some were retrospective; and many only included a modest proportion of their TIA population (e.g. 53%[59]) (so may be prone to selection and small study bias). Many studies suggested that having a lesion on DWI (versus not having a lesion) predicted increased risk of subsequent stroke,[59-62] but others found that lesions on DWI matched the same clinical features that are predictive of stroke after TIA and are already predicted by clinical scoring.[48;63] Whilst having a lesion on DWI was an

independent risk factor for stroke in some studies,[59-62] several others failed to confirm this independent association[63] and instead found that clinical features and carotid stenosis were stronger predictors.[58;62] However, the accuracy of the widely publicised ABCD and ABCD2 clinical scores22 in predicting stroke risk has recently been questioned,[30;64] so DWI could add prognostic as well as diagnostic value after all. Furthermore, for the published literature of the diagnostic and prognostic utility of MR, we cannot exclude the possibility of publication bias. Finally, the focus on DWI has overlooked the contribution of other MR sequences to identifying recent and old haemorrhage and its accuracy in detecting stroke mimics (which may be no better than CT).

The problems with MR. The available data are limited by the study methodological factors, listed above. MR is also much more expensive than CT scanning (about £400 for MR versus £150 for CT brain scanning.)[11] It is still in very short supply in the UK, with long waiting lists even for patients with established indications for MR. Thus, there is very limited capacity to provide rapid access to MR for people with TIA and stroke (MR delayed even by a few days is of little value since the patient will miss the window of opportunity to have preventive treatment during the early days of highest risk).[65] Although 75% of UK hospitals had MR on site, less than 10% were able to scan patients early after stroke.[65] The UK is not alone in this as across the EU, only 5% of hospitals met criteria for stroke care which included availability of MR for stroke (and surprisingly the UK had the highest proportion of hospitals with MR for stroke).[66] Any increase in use of MR for stroke prevention could result in reduced availability for - for example - patients with cancer, where MR is of established benefit. Some patients cannot have MR because of contraindications, e.g. having a pacemaker, claustrophobia or metal implant, so there would always be a need for CT. In one recent study, only 90/904 patients [12%] considered for MR had contraindications and only 477/904 (53%) of all patients presenting with TIA actually underwent MR; of those having MR only 155/477 (33%, or 17% of the initial cohort) had a DWI-positive lesion. The accuracy of MR for common mimics of TIA/minor stroke is unclear as most publications excluded patients who turned out after further testing not to have had a stroke. Not all TIA patients have CT at present, so MR including DWI would partly replace, and partly be an additional investigation, if it proved to be cost-effective in improving the management of TIA.

Are guideline statements supported by robust evidence? The limited evidence has lead some reviewers to call for more data on imaging to guide physicians treating TIA patients.[67;68] The NHS Purchasing and Supply Agency 2008 report stated only that “DWI shows significant potential in the study of TIA/minor stroke”, but also called for “more evidence”.[69] Despite this – rather surprisingly - the 2008 UK Stroke Strategy guidelines and the National Institute for Health and Clinical Excellence (NICE) guidelines advocate use of DWI in either 50% of[70] or most[71] TIA/minor stroke patients (www.dh.gov.uk/stroke). The American Heart Association and related organisations stated that “TIA patients should undergo neuroimaging evaluation within 24 hours of symptom onset, preferably with magnetic resonance imaging including diffusion sequences”.[72] The revised National Clinical Guidelines for Stroke,[73] SIGN Guidelines 2008,[74] and European Guidelines[75] are more cautious but still advocate immediate brain imaging and use of MR including DWI in large proportions of patients especially those with mild stroke. The guidance tends to overlook the need for other sequences to identify haemorrhage and stroke mimics, hence there is a need for further work to define the accuracy of MR for all aspects of stroke diagnosis and the incremental difference, if any, from the accuracy of CT. Therefore, there is a ‘mismatch’ between national and international guidance on the one hand,[70;72] and convincing evidence to support this approach,[48;49] information to guide precise usage,[69] details of cost-effectiveness and available technology to deliver it on the other,[65;66] resulting in confusion about what to do in routine practice.

Summary: ***Potential benefits.*** MR including DWI and other relevant sequences, could make a substantial impact as a positive diagnostic test for TIA/minor stroke by: improving diagnosis of the cause of stroke; efficient patient selection for medical secondary prevention in patients with a proven diagnosis; conversely, the avoidance of unnecessary treatment in patients in whom acute ischaemic cerebrovascular disease was reliably excluded; and best use of carotid endarterectomy (especially where stroke expertise is limited). ***Potential cost implications.*** TIA/minor stroke is so common that MR including DWI and other relevant sequences would be in daily use in every hospital if such a strategy were adopted, but the direct costs to the NHS would be substantial - £16 million per year to scan just the 50% of TIA patients suggested in recent UK guidelines, not including the minor strokes and all the TIA mimics, assuming that MR were available. ***Opportunity costs.*** The opportunity cost to meet the demand by increasing MR scanning capacity, (without which there would also be substantial disadvantage to other MR users). ***Overall cost-effectiveness unclear.*** It is not clear if the potential diagnostic and prognostic advantages of MR outweigh the disadvantages of the obvious expense, limited availability, failure to make a positive diagnosis of ischaemic lesion in up to 66% of TIA patients, unquantified accuracy for other stroke-related diagnoses, and possibility that the strokes that we are trying to prevent might occur during the wait for a scan if availability cannot be rapidly increased. Any strategy to increase MR usage would have to factor in the effect of varying delays introduced because of waiting for MR. We are not aware of any large or multicentre studies ongoing on this topic, although it is likely that single centre studies are ongoing. The proposed study aims to resolve this controversy by summarising all available data on MR including DWI and other relevant sequences, diagnosis and stroke prediction, and model the cost-effectiveness of increasing MR including DWI and other relevant sequences usage to existing stroke prevention strategies.

6. Plan of Investigation

Design: The study is an evidence synthesis of literature data, surveys of practice and costs, and health economic modelling with sensitivity analyses of important variables (see Diagram).

1) Systematic review: We will systematically review the literature to: estimate the sensitivity/specificity of CT and MR including DWI and other relevant sequences in TIA/minor stroke, including the arterial territory; to assess their role in prediction of stroke after TIA; to estimate costs of CT and MR (summarised to 2003 in[35] but requiring updating); and to gather all data required to model stroke prevention after TIA. All aspects of the systematic review, including literature searching, quality assessment, data extraction, and evidence synthesis will be performed according to the Cochrane Collaboration and Stroke Group standards, including recommendations from the Screening and Diagnostic Tests Methods Group, as in previous work.[11;42] The methods for evidence synthesis (meta-analyses performed according to the summary receiver operator characteristic (SROC) curve methodology or separate meta-analyses of sensitivity and specificity estimates) will be contingent on the data obtained and the most appropriate method will be used.[76] We will use a standardised quality assessment instrument (i.e. the Quality Assessment of Diagnostic Studies tool - QUADAS),[77] with modifications as appropriate as in previous work.[35;78]

2) We will obtain data on demographics, risk factors, medications, recurrent stroke and death in patients with TIA/minor stroke relevant to the UK in order to construct the health economic model. We will use existing datasets where possible, e.g. large stroke and TIA registries,[79] individual patient datasets, and routinely collected anonymised national audit data, as in previous work.[11;35]

3) We will systematically review the literature for data on costs of CT and MR in the UK and other countries with relevant healthcare systems (data available to us from previous HTA-funded projects will help this process but requires updating). We will

obtain up to date imaging costs from the NHS Department of Health NHS Reference costs database and NHS Scotland Information and Statistics Division (ISD) Costs Book. We will also obtain specific up to date costs of diagnostic imaging for stroke with CT and MR from individual radiology departments in a range of hospitals in the Scottish Imaging Network - A Platform for Scientific Excellence (SINAPSE) Collaboration, which includes six University centres including four regional specialist neuroscience centres and networks with district general hospitals in different large and small cities. Together, these costs will provide a realistic range of current costs for the health economics model and information on which to base sensitivity analyses of the effects of higher or lower costs on the outcome of the health economics modelling as in previous work.[11;35]

4) We will survey UK stroke physicians through the British Association of Stroke Physicians as in previous work[11] to ask about stroke prevention clinics including current access to and use of MR sequences, including DWI and other relevant sequences in patients with TIA/minor stroke in the NHS, aspirations and consensus on role of MR, and to gather additional unpublished data on MR including DWI and other relevant sequences in TIA/minor stroke.

5) We will survey UK radiology departments through the SINAPSE Collaboration in Scotland, and the College of Radiologists and British Society of Neuroradiologists elsewhere in the UK to determine what capacity there is for increased throughput of TIA and minor stroke patients, and to identify the perceived major barriers to increased or faster throughput of TIA/minor stroke patients and what additional resources would be required to provide additional access for these patients.

6) We will obtain UK data on the health care costs associated with management of stroke patients by literature review of relevant electronic databases such as Medline, Embase and SCOPUS,[80] and interrogation of specific sources such as stroke registry data as in previous work (see below for specific details)[11;35]

7) We will obtain data on quality of life after stroke for key subgroups from the literature and from our previous work and from our local stroke register data.[81]

8) We will build a model that reflects key stages and outcomes in secondary stroke prevention after TIA/minor stroke, including all data on assessments, medical and surgical interventions, outcomes, and timings, populated with representative data from TIA/stroke services in the UK. The timelines in the model will be stratified by time after symptoms, key patient characteristics, use of prognostic scores (ABCD2)[22] including conventional investigations (CT, carotid imaging) and treatment decisions, and key outcomes of non-disabling and disabling stroke and death at six months, one and five years.

9) We will model the incremental cost-effectiveness of implementing MR including DWI and other relevant sequences instead of usual care in the diagnosis of TIA/minor stroke. The clinical outcomes of non-disabling stroke, disabling stroke and death will be summarised through the calculation of Quality Adjusted Life Years (QALYs). QALYs will be calculated by the generation of quality of life weights for disabling and non-disabling stroke, and the assignment of probabilities to these outcomes. Literature review and statistical modelling of registry data will inform the calculation of probabilities of clinical outcomes with and without MR including DWI and other relevant sequences. Quality of life weights will be based on values from published literature and, where feasible, registry data. The definition of usual care will be developed following literature review of current UK studies and interrogation of stroke registry data; however, following previous work it is anticipated that it will be based on CT scanning varying proportions of cohorts of 1000 patients presenting to hospital with suspected TIA/minor stroke. Modelling will account for patient heterogeneity; e.g. in spite of increased efforts to raise awareness of the importance of acting quickly on noticing stroke symptoms, a proportion of patients with TIA/minor stroke may continue to present late after symptoms. In these patients, CT scanning will not identify the small proportion (5%) who have a small haemorrhage as the

cause of their stroke and MR scanning is required.[37] We have already analysed the sensitivity and specificity of CT and MR for haemorrhage in patients presenting beyond five days after symptoms[35] but did not perform a cost-effectiveness analysis of increased use of MR in this predominantly out patient population. Therefore it is anticipated that cost-effectiveness will be measured separately for both 'early' and 'delayed' presentation of symptoms, with 'delayed' defined as presenting over five days after stroke. To test the robustness of the point estimates generated and to quantify the degree of decision uncertainty, probabilistic sensitivity analysis (PSA) will be conducted. This will involve taking repeated random draws from specific distributions of all stochastic parameters (clinical outcome probabilities, relative risk reduction of associated events with MR DWI and other relevant sequences, usual care quality of life score, disabling and non-disabling stroke quality of life score, usual care health care costs, and imaging costs). The output from the PSA will then be used to calculate the probability that the new diagnostic strategy is more cost-effective than usual care. Value of information analysis will be conducted to investigate the worth of commissioning further research on the cost-effectiveness of MR DWI imaging and inform the design of any future research. Population Expected Value of Perfect Information (EVPI) will be computed to assess whether the benefits of future research in the form of reduced uncertainty exceed the likely costs of research, and to assess which parameter, or set of parameters, should be the focus for any future research; analysis of covariance techniques will be used to explore the proportionate contribution of each parameter to variation in incremental cost and QALYs. Further, the EVPI for parameters will be calculated, in which repeated model simulations will be run with each parameter held constant in turn, whilst allowing other stochastic parameters to vary, so as to provide clinically-relevant data on key age groups, stroke risk strata and MR availability. All modelling work will be performed according to recommended guidance (http://www.equator-network.org/).[82] 10) Finally, using information on investigation costs, we will estimate the effect of using MR or CT also to diagnose carotid stenosis as a 'one stop' investigation, instead of performing the MR or CT brain scan and separately performing carotid imaging with, for example, ultrasound. This will reflect the reality that different imaging modalities are used in different centres for reasons of equipment availability. We have already determined the accuracy and cost-effectiveness of different carotid imaging tests in the diagnosis and management of carotid stenosis in stroke prevention.[11;46] However, we have not assessed the cost and practicality of performing 'one stop' brain and carotid imaging. Obtaining all the information required from imaging in one scan is attractive, but factors such as increased machine occupancy, radiation dose (CT), patient unacceptability (MR), and contraindications to contrast agents required for the carotid imaging (both CT and MR) will limit the number of patients who can actually have 'one stop' brain and carotid imaging. We will use data from our previous HTA report[11] combined with updated information on accuracy of carotid imaging,[83] data on practicality from Glasgow Neuroradiology where CT with CTA (rather than CT plus ultrasound) is the routine investigation for suspected carotid stenosis and the cost information that we will obtain in the present work, to examine the effect of replacing traditional separate brain and carotid imaging tests with 'one stop' CT or MR imaging. In this analysis, the base case scenario will be CT brain scan and carotid ultrasound.

Planned inclusion/exclusion criteria: We will model a typical population of patients presenting with suspected TIA/minor stroke based on existing data as in previous work, updated to reflect current demographic, pre-stroke medications, and stroke treatments using information from the literature and a large national stroke audit. These include: the North Edinburgh Stroke Study and Lothian Stroke Register (n= 2598, a hospital-based registry of all in and out patients with TIA and stroke presenting to our hospital between 1990 and 2000 with demographic information, imaging and laboratory investigations, past medical history, medications prior to and

following the TIA/stroke, and quality of life data) and followed up to four years for recurrent stroke, cardiac events and death and used in two previous HTA reports;[11;35] the Edinburgh Stroke Study (n= 1367, a hospital-based registry of all in and out patients with TIA and stroke presenting to our hospital between 2002 and 2005 with the same information except quality of life) and so far followed up to four years after the stroke;[79] and the Incidence of Stroke in the Lanarkshire Area (ISLA) study (K Muir). We will obtain longer term follow-up for stroke, other major vascular events and death for both cohorts at the start of the project through data linkage with the ISD (http://www.isdscotland.org). We also have data from other studies of stroke and TIA with more detailed imaging, including a study comparing CT and MR scans in minor stroke between 1998 and 2001 (n=230),[37] a study of patients with mild cortical and lacunar stroke between 2005 and 2007 (n=250),[84] and a study of practicalities and workload implications of increased use of MR imaging in patients with TIA in Glasgow (K Muir ongoing). Other population-based studies of TIA/minor stroke which may provide additional details are available to us and additional new data may become available from other stroke prognosis studies. The Scottish Stroke Care Audit (SSCA) routinely collects data from hospitals across Scotland that provide stroke services (PI M Dennis). Data from SSCA will be routinely linked through ISD to provide anonymised data on the process of stroke care across the Scottish population in late 2009 (project currently underway jointly run by SSCA and ISD, with a research governance committee to guide access and usage). We will apply to use anonymised data from the linked audit to provide up to date population-based data that reflect current stroke care. We will stratify data in the model by age, underlying vascular risk factors, sex, prior use of medical treatments, and other factors which may affect stroke risk and therefore require data with this degree of granularity for the model.

Ethical arrangements: The use of existing anonymised data to populate the model and perform other analyses does not require additional ethics approvals. We will apply to the ISD Privacy Advisory Committee for permission to link the LSR and ESS data (this has been done previously and no current problems are anticipated with repeating this request). We will also apply to the new committee which is being formed to review requests for use of ISD-linked data from SSCAS (see above). All data used in the proposed modelling will be anonymised.

Proposed sample size: We will model the effect of incremental change in proportions of TIA/minor stroke patients undergoing MR imaging for a typical UK population of 1000 patients as performed previously in HTA-funded projects assessing the cost-effectiveness of CT scanning in acute stroke[35] and of carotid imaging in stroke prevention.[11] We have several existing datasets including several 1000 patients with TIA, minor and major stroke, with initial clinical and imaging assessment, and data on functional status, stroke recurrence and death at six months, one year and four years, which we propose to data link with centralised health care statistics as details above. We will provide the results in the form of "events per a cohort of 1000 patients presenting to hospital with suspected TIA and minor stroke".

Statistical analyses*: Systematic review of diagnostic accuracy*: Indices of diagnostic performance will be extracted or derived from data presented in each primary study for each imaging test. Where data are available, we will construct 2 X 2 contingency tables of test results versus reference standard to show the cross-classification of disease status and test outcome. We will calculate sensitivity and specificity with 95% confidence intervals for each imaging test for each study. To describe and visualise the data, we will draw forest plots showing the pairs of sensitivity and specificity estimates for each study. For a descriptive analysis we will also plot the imaging test results on a receiver operating characteristic (ROC) plot of true positive rate (sensitivity) against false positive rate (1 - specificity). The choice of statistical methods to combine studies will depend upon the pattern of heterogeneity observed

between study results. Where appropriate, we will pool data from included studies using SROC curve methods,[84] which are based on a random effects approach and take into account the degree of heterogeneity between studies. Where possible, co-variates will be incorporated in the SROC model to examine the effect of potential sources of heterogeneity on sensitivity and specificity estimates. If the SROC model proves inappropriate we will summarise results using univariate meta-analyses of true and false positive rates.[76]

Economic modelling: Data from included studies will be appraised, summarised, and interpreted alongside the results of the systematic review of diagnostic accuracy so that conclusions will be drawn on the effect of MR including DWI and other relevant sequences compared with the current alternative of CT brain scanning, as detailed in 9 above.

Proposed outcome measures: The primary outcome will be the incremental cost-effectiveness of MR scanning compared with the reference standard. Proposed secondary outcome measures include: the estimates of sensitivity/specificity of 'MR including DWI and other relevant sequences' versus 'conventional clinical assessment plus CT' to diagnose TIA/minor stroke; the proportion of patients with TIA/minor stroke with a visible ischaemic lesion on 'MR including DWI and other relevant sequences' and CT brain scanning and the association with key clinical variables; whether adding information from brain scanning to clinical risk scoring improves prediction of future risk of stroke or death; the association between a positive or negative brain scan and risk factors for stroke such as carotid stenosis; delays to diagnosis, delays to starting medical or surgical treatment if MR including DWI and other relevant sequences were to replace CT brain scanning; the number of disabling strokes prevented at six months, one and five years after TIA/minor stroke if 'MR including DWI and other relevant sequences' were to be used in most patients for a cohort of 1000 patients; quality adjusted life years stratified by key patient groups (e.g. elderly); the cost-effectiveness of substituting MR including DWI and other relevant sequences for CT brain scanning in patients with TIA/minor stroke in important demographic subgroups and by different times to presentation; and an estimate of the increase in availability of MR for TIA/minor stroke that would be required (if any) to accommodate TIA/minor stroke patients rapidly after the index event. We will provide a range of options reflecting effect of using MR in different proportions of TIA/minor stroke patients to guide decision-making by health service purchasers.

7. Project timetables and milestones

We anticipate that the project will take 18 months to be completed.

Month 1-2: Appoint staff, develop a protocol, develop literature searches, design data extraction forms, discuss structure for model;

Month 3-8: Diagnostic review, economic review and model development, design survey questionnaire, survey stroke prevention clinics;

Month 9-12: Test model, writing up diagnostic review;

Month 12-14: Modelling (run model and sensitivity analyses);

Month 14-18: Report writing and papers preparation.

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