The 2nd European Carotid Surgery Trial (ECST-2)

Protocol

Version 3.1

11 November 2015

International Standard Randomised Controlled Trial Number: ISRCTN97744893

CONTENTS

PROTOCOL SUMMARY

BACKGROUND Randomised trials have established the benefit of revascularisation by carotid endarterectomy (CEA) for moderate and severe carotid stenosis. However, a risk model derived from one of these trials and validated in another, showed that only patients with a high risk of stroke under medical therapy benefited from CEA. For a large range of patients there was neither clear benefit nor harm from CEA. Medical therapy for stroke prevention has improved since these original trials, with more widespread use of statins, more active lowering of blood pressure and more effective antiplatelet regimes. Lower optimum targets have been set for risk factor control e.g. blood pressure. Therefore CEA may not be beneficial in many patients with carotid stenosis treated by modern optimized medical therapy (OMT).

HYPOTHESIS We hypothesize that in patients with carotid stenosis at lower risk for stroke, OMT alone is as effective in the long-term prevention of cerebral infarction and myocardial infarction (MI) as revascularisation and OMT combined.

STUDY DESIGN ECST-2 is a multicentre, randomised, controlled, open, prospective clinical trial with blinded outcome assessment. We will use a risk model based on clinical characteristics to calculate a 5-year Carotid Artery Risk (CAR) score, which will stratify patients as at high risk (≥20%) or lower risk (<20%) of future stroke using predictive data from previous trials recalibrated to take account of the likely benefit of OMT. An interim analysis using MRI to determine the 2-year rates of cerebral infarction and haemorrhage after randomisation will be performed to assess safety and feasibility of the design and inform the design and sample size calculations for the full trial. ECST-2 will incorporate baseline imaging of carotid plaque where possible to investigate the predictive value of plaque characteristics.

CENTRE REQUIREMENTS A neurologist or physician with an interest in stroke; a surgeon with expertise in CEA; if available, an interventionist with expertise in CAS. Access to MRI.

INCLUSION CRITERIA Patients with symptomatic or asymptomatic atherosclerotic carotid artery stenosis (> 50%, NASCET criteria), suitable for revascularisation with CAR score indicating risk <20%.

MAIN EXCLUSION CRITERIA Patients with a CAR score indicating high risk, patients refusing either treatment, unable to consent or unsuitable for revascularisation due to anatomy, ill-health or disabling stroke (current Rankin >2). Recent contralateral carotid revascularisation, cardiac or other major surgery.

RANDOMISATION AND TREATMENTS Patients will be randomly allocated in equal proportions to be treated by 1) immediate carotid revascularisation with OMT or 2) OMT alone (in the latter arm, revascularisation may be performed at a later stage if it becomes more clearly indicated e.g. because of TIA during follow up). Randomisation will be stratified by centre, type of planned revascularisation, symptom status and CAR score. A web-based randomisation system will be used. We anticipate that revascularisation will be by CEA in most patients, but carotid stenting (CAS) may be used if considered more appropriate. Centres will prespecify whether a patient will receive CEA or CAS if allocated to revascularisation. Randomisation and analysis will be stratified by the pre-specified intervention. The randomisation form will include entry of data to confirm a CAR score of <20%. OMT in both arms will consist of all three of: 1) optimal antiplatelet therapy; 2) statin or other cholesterol lowering treatment with target total cholesterol of <4 mmol/l and LDL cholesterol of <2 mmol/L; 3) antihypertensive treatment, if required, with target blood pressure of 135/85 mmHg. Patients will also undergo risk factor modification e.g. advice on smoking.

FOLLOW UP The planned duration of follow up is a minimum of 5 years up to a maximum of 10 years. Recruitment and follow up will be supervised by the neurologist or stroke physician. Follow up will include ECG and troponin at 48 hours after revascularisation, with MRI at baseline and at 2 and 5 years follow up.

SAMPLE SIZE The planned sample size is 320 patients for the safety MRI analysis and 2000 patients for the full trial.

PRIMARY OUTCOME MEASURES For the full trial: any stroke at any time, plus non-stroke death occurring within 30 days of revascularisation. For the safety MRI analysis: The combined 2-year rate of cerebral infarction, cerebral haemorrhage, MI or periprocedural death after randomisation as assessed by follow up MRI and screening for MI.

SECONDARY OUTCOME MEASURES Ipsilateral stroke, myocardial infarction, transient ischaemic attack or any hospitalisation for vascular disease during follow up. Disabling stroke during follow up. New cerebral infarction or haemorrhage on post procedural MRI. Ipsilateral restenosis or stenosis progression. Cognitive impairment. Further treatment procedure. Adverse events attributed to medical treatment or CEA. Quality of life and economic measures.

ECST-2 PROTOCOL

BACKGROUND

Risks of carotid endarterectomy and optimal medical therapy compared

Atherosclerotic stenosis of the carotid artery causes about 15% of ischaemic strokes. Carotid endarterectomy (CEA) to prevent stroke has become the commonest operation performed in stroke patients. The first European Carotid Surgery Trial (ECST) and the North American Carotid Endarterectomy Trial (NASCET) established the benefit of CEA in preventing stroke in patients with symptomatic carotid stenosis of >50% measured using the NASCET method [1,2]. The results led to guidelines recommending CEA for patients matching the characteristics of the trial patients. However, CEA carried a risk of peri-operative stroke or death of around 7%, and can also cause myocardial infarction (MI) as a consequence of surgery. Moreover, CEA did not prevent all recurrent strokes. A risk model derived from ECST and validated in NASCET showed that only patients with a high risk of subsequent ipsilateral stroke when treated medically (5-year risk >20%) benefited from CEA, while patients with a lower risk of stroke did not benefit significantly [3,4] because the benefit of surgery in the longer-term prevention of stroke did not justify the perioperative risk of stroke or death.

Asymptomatic carotid stenosis of >60% had a low 5-year risk of stroke of 11% treated medically in the Asymptomatic Carotid Surgery Trial (ACST), and the trial only showed only a small overall benefit of CEA [5]. ACST has been interpreted by many surgeons as strongly favouring CEA, which is now one of the commonest operations in the USA (250,000/annum, 92% asymptomatic) [6]. In the UK, surgeons have been less enthusiastic, but increasing numbers of patients with asymptomatic stenosis are receiving CEA. In a UK wide audit published in 2012, 13% of CEAs were performed for asymptomatic stenosis [7]. However, many physicians consider that the evidence does not support a policy of CEA for asymptomatic stenosis and instead patients would be better off being treated with modern medical therapy [8]. The differences in opinion illustrate current uncertainty about the indications for CEA.

Medical therapy for prevention of stroke in patients with carotid disease has evolved since the original trials e.g. widespread use of statins, lower targets for blood pressure (BP) control and more effective antiplatelet regimes. Statins were not available in ECST or NASCET. In ACST, statins were used by only 17% in the first 4 years of the study [5]. Subgroup analysis from randomised trials and case control studies have shown that statins lower stroke risk in patients with cerebrovascular disease by about a third and halve the numbers requiring CEA [9-11].

Antiplatelet therapy has changed from aspirin alone, to the combination of aspirin with dipyridamole, or clopidogrel. BP control has also improved. None of the previous trials incorporated targets for BP or cholesterol levels, which can be expected to improve control further. Observational studies and systematic reviews suggest a fall over the last 20 years in the annual risks of stroke following the finding of asymptomatic carotid stenosis, most likely explained by improvement in medical risk factor control [12,13]. We therefore hypothesise that the routine use of modern optimised medical treatment (OMT) aimed at achieving target levels of blood pressure and serum cholesterol and combined with targeted risk factor modification, will halve the rate of stroke in patients with carotid stenosis during follow up, obviating the need for endarterectomy in many patients with carotid disease. In contrast, a systematic review published in 2009 concluded that there is no evidence of a fall in operative risks for CEA over the last two decades, with 30-day stroke or death rates in neurologist assessed cases being 5.6% in studies between 2001 and 2008 [14]. However, in our recent trial, the International Carotid Stenting Study (ICSS), the 30-day risk was lower at 3.4%. Hence, the risks from carotid surgery may have improved in our centres, but the absolute reduction is likely to be much less than the improvement associated with OMT. We therefore hypothesise that in patients at lower risk for stroke, OMT alone will be as effective as early revascularisation plus OMT in preventing long term stroke, taking into account the additional risks of periprocedural stroke or death associated with revascularisation.

Carotid stenting

Since the original trials of CEA were completed, carotid stenting (CAS) has become a popular alternative to endarterectomy for atherosclerotic stenosis of the carotid artery in some centres. Four large randomised studies (SPACE, EVA-3S, ICSS and CREST) comparing the safety and efficacy of carotid stenting versus endarterectomy have recently published short term outcomes and some longer term results [15-20]. SPACE failed to demonstrate non-inferiority of stenting compared with endarterectomy [16], while EVA-3S and ICSS showed a significantly higher rate of peri-procedural stroke or death in the stenting group [18,19]. CREST showed no significant difference in the combined primary outcome measure of periprocedural stroke, death or MI or ipsilateral stroke during follow-up, but unlike the other trials included significant numbers of patients with asymptomatic stenosis [20]. Analysis of the CREST results limited to patients with symptomatic stenosis showed a significant excess of stroke or death within 30 days of CAS compared with CEA. A recent metaanalysis [21] of pooled individual data from three trials (SPACE, EVA-3S and ICSS) enrolling patients with symptomatic stenosis found evidence that in the short-term, the relative harm of stenting compared with endarterectomy decreases with younger age; in patients <70 years old the estimated 120 day stroke or death risk was virtually identical at 5·8% in those allocated CAS and 5·7% in those allocated CEA (RR 1·00 [0·68-

1·47]). All the excess risk of CAS appeared to be in patients 70 years or older, where the risk of CAS vs CEA was 12·0% versus 5·9%, (RR 2·04 [1·48- 2·82]).

The data from the large randomised trials therefore shows that overall endarterectomy is the treatment of choice for carotid stenosis, but nevertheless stenting remains an option for revascularisation of atherosclerotic carotid stenosis in patients less suitable for CEA or unwilling to undergo surgery, and might also be an offered to younger patients as an alternative to surgery in centres with considerable experience and good results from carotid stenting. Since the risks of CAS, in appropriate patient subgroups, are equivalent to those of surgery, we also hypothesize OMT alone will be as effective in the long-term prevention of stroke as stenting and OMT combined in patients at lower risk for stroke. ECST-2 will include patients in whom it is planned that carotid revascularisation would be performed by stenting, so long as the local clinicians consider CAS is preferable to CEA in the individual patient after multi-disciplinary discussion. Given the uncertainty about the indications and numbers of patients who will receive CAS in the future, data from patients in whom stenting is planned will be analysed separately.

Use of MRI as an outcome measure

Magnetic resonance imaging (MRI) using diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences is much more sensitive than clinical assessment in detecting ischaemic brain lesions after carotid interventions and identifies cerebral infarction in patients without overt symptoms or signs. 2000 patients in the population based Rotterdam study were examined with Brain MRI and 2% of these were found to have asymptomatic cortical brain infarcts and 5.5% asymptomatic lacunar infarcts.[22] In another study based on a subset of 810 middle-aged persons without clinical stroke or baseline magnetic resonance imaging infarct enrolled in the Atherosclerosis Risk in Communities Brain Magnetic Resonance Imaging Study, 20.2% of participants developed cerebral infarcts over a median of 10.5 years follow up.[23] As well as occurring spontaneously, silent ischaemic lesions on MRI are found with increased frequency after minor stroke and transient ischaemic attack (TIA); in one study there was a 10% risk of new lesions on MRI half of which were asymptomatic.[24] Kang et al [25] looked at the recurrence of silent lesions on MRI at 30 and 90 days after acute ischaemic stroke and found this to be 22%, and these lesions predicted recurrent ischaemic stroke, transient ischemic attack, or vascular deaths. Silent infarcts detected on MRI are also seen after revascularisation procedures.[26,27]. In the MRI substudy of the International Carotid Stenting Study (ICSS), we showed that about three times more patients in the stenting group (50%) than in the endarterectomy group (17%) had new ischaemic lesions on post-treatment MR scans one day after treatment, a difference that was statistically highly significant and persistent infarction on FLAIR imaging after one month was found in 33% and 8% of patients,

respectively.[28] The results mirrored the main results of ICSS which showed a significantly higher rate of symptomatic stroke from stenting, but required a sample size of 1,713 patients to show a significant difference, compared with the 231 patients necessary to show a significant difference in the ICSS-MRI substudy. The total volume of infarction, i.e. adding together different focal areas of infarction on MRI, correlated with the occurrence of reported focal neurological signs. Furthermore, the differential risk of cerebral ischaemia between CAS and CEA was modified by risk factors e.g. the type of the most recent ipsilateral event before randomisation. It has also been shown in patients with asymptomatic middle cerebral artery stenosis that treatment with simvastatin significantly reduces the occurrence of new lesions on MRI.[29] In addition, even in the absence of signs and symptoms of infarction, silent lesions may be associated with an increase in the rate of cognitive decline with age and the development of dementia.[30]

Thus MRI detects cerebral infarcts in the absence of clinical signs and symptoms, both occurring as a complication of revascularisation procedures and accumulating in patients treated medically for cerebrovascular atherosclerosis. MRI has the additional advantage that the scans can be reported blind to clinical details avoiding the risk of ascertainment bias. The ICSS-MRI substudy also demonstrated that the differential risk of cerebral ischaemia was modified by risk factors e.g. the type of the most recent ipsilateral event before randomisation. Furthermore, MRI may provide valuable data for improving risk models to identify patients' suitability for a given intervention.

Therefore, we propose screening patients during follow up using MRI in ECST-2 to objectively determine rates of cerebral infarction and haemorrhage. Our main MRI outcome measure, any new ischaemic brain lesion two years after study entry, will compare the safety and long-term efficacy of invasive revascularisation versus conservative treatment of cerebrovascular atherosclerosis. We will also compare the total volume of cerebral damage detected by MRI between the treatment arms.

OBJECTIVE

We propose that in the future it would be better if patients were routinely selected for revascularisation on the basis of a detailed, up to date risk assessment taking into account all the known risk factors. However, for this to be accepted we need to confirm the accuracy of our risk assessment model in the context of modern medical management in symptomatic and asymptomatic stenosis, and assess the current risks and benefits of carotid revascularisation in these patients.

AIM AND HYPOTHESIS

The aim of ECST-2 is to determine the best current regime for treating patients with asymptomatic and symptomatic carotid stenosis who are at lower risk of stroke. Our main hypothesis is that patients who have clinical characteristics that predict a 5-year risk of future ipsilateral stroke of <20% when treated with modern optimized medical treatment (OMT) alone, will not benefit from early revascularisation in addition to OMT, because any reduction in future stroke rates after revascularisation will be balanced by an excess of procedural stroke and death.

TRIAL DESIGN

The proposed study is a multicentre, randomised, controlled, open, prospective clinical trial with blinded outcome assessment. An interim analysis will be performed after recruitment and follow up of 320 patients to assess the safety of the treatment policies and inform the design and sample size calculations for the full trial, using MRI to determine rates of cerebral infarction and haemorrhage at 2 years after randomisation. This interim analysis will provide an opportunity to assess the following aspects of the study:

1. Is our design of trial acceptable to clinicians, patients and carers?
2. Can we achieve recruitment rates in line with our previous trials and recruit 320 patients by the end of 3 years?
3. Can our centres easily and correctly apply the risk model using a web-based service to select patients for randomisation?
4. Can our investigators and participating patients achieve medical treatment targets for blood pressure and cholesterol levels and other risk factor reductions without unacceptable side effects?
5. Does the data from MRI provide any evidence of a major difference between the treatment arms?

Any difficulties with our design or randomisation service during this initial phase will be noted and used to refine the protocol for the full scale trial. Similarly, relevant findings from the MRI analysis may be used to modify the risk model. The recorded rates of outcome events during the pilot phase will be used to check on the accuracy of our predictions and modify the proposed sample size for the full trial if required.

PARTICIPATING CENTRE REQUIREMENTS

Each centre must have a neurologist or physician with an interest in stroke to see patients prior to randomisation and to supervise follow up. Centres should have a process for ensuring that the management of individual patients with carotid stenosis is routinely discussed between the neurologists or stroke physicians, surgeons, and radiologists or interventionists enrolled as investigators in the trial e.g. multidisciplinary meetings. Each patient included in ECST-2 must be discussed before being randomised in the trial. Carotid endarterectomy (CEA) must be carried out by designated surgeons with expertise in the operation. Similarly, in centres planning to offer carotid stenting, this must be carried out by a designated and appropriately qualified interventionist. Centres will be required to submit documentation demonstrating the training and experience of their investigators, together with an audit of the outcomes of carotid revascularisation at their centre. A credentialing committee will be responsible for approving individual centre enrolment on the basis of this documentation and any other information requested by the committee. Where a surgeon or interventionist does not adequately meet the committee's requirements, they may still be able to join the trial if proctoring by an approved specialist in the relevant procedure can be agreed and arranged for their initial trial procedures.

ETHICAL APPROVAL

The trial protocol has ethics and NHS approval from the National Research Ethics Service in the UK after review by the NRES Committee East of England, Cambridge Central. Individual centres in the UK will be required to have local R&D approval before randomising patients. Outside of UK, ethics approval will be required according to local arrangements.

INCLUSION CRITERIA

- Patient is aged over 18 years of age
- Symptomatic or asymptomatic atherosclerotic carotid stenosis of at least 50% calculated using criteria equivalent to the NASCET method.
- Patients with a carotid artery risk (CAR) score indicating a 5 year ipsilateral stroke risk of <20%.
- Patient is medically and neurologically stable and suitable for CEA or CAS.
- Clinicians are uncertain about which treatment modality is best for the individual patient.
- Patient is able and willing to give informed consent.

EXCLUSION CRITERIA

- Patients unwilling to have either treatment modality.
- Patients unwilling or unable to participate in follow up for whatever reason.
- Patients with a modified Rankin score (mRS) greater than 2 for any reason. Such patients may be eligible for inclusion at such time as they improve to a mRS of 2 or less
- Patients who are medically or neurologically unstable or have progressing neurological signs. Such patients may be eligible for inclusion at such time as they become stable.
- Patients who have had coronary artery bypass grafting within 3 months prior to randomisation or other major surgery within 6 weeks prior to randomisation.
- Patients in whom it is planned to carry out coronary artery bypass grafting or other major surgery within 6 weeks after the planned CEA or CAS of the artery being considered for treatment in the trial.
- Patients with a CAR Score ≥20% or other reason for believing the patient would get clear benefit from CEA or CAS.
- Occlusion of the ipsilateral carotid artery considered for randomisation (contralateral carotid artery occlusion is not an exclusion).
- Patients not suitable for either surgery or stenting due to anatomical factors e.g. long segment disease extending to the distal cervical carotid/skull base.
- Intraluminal thrombus within the carotid seen on ultrasound or angiography.
- Carotid stenosis caused by non-atherosclerotic disease e.g. dissection, fibromuscular disease or neck radiotherapy.
- Previous CEA or CAS in the artery to be randomised.
- Recent revascularisation of the contralateral carotid artery or a vertebral artery or an intracranial artery carried out within 6 weeks prior to date of randomisation. The patient can be randomised if still suitable once the 6 week period has elapsed.
- Planned revascularisation of the contralateral carotid artery or a vertebral artery or an intracranial artery within 6 weeks after randomisation or 6 weeks after the date of allocated ipsilateral carotid revascularisation. Thereafter, these arteries may be treated by revascularisation.
- Patients who are known to be pregnant.
- Patients who have a life expectancy of less than two years due to a pre-existing condition e.g. cancer.
- Patients intolerant or allergic to all of the medications available for optimised modern medical therapy.
- Patients in clinical trials of investigational medicinal products (CTIMPS) or who have been in a CTIMP within the last 4 months will not be enrolled unless otherwise agreed.

Patients in other research trials (both stroke related and non-stroke related) may be enrolled where this would not conflict with the treatments used in ECST-2 or place undue additional burdens on the patient. A list of such trials approved by the TSC will be available on the trial website. Before enrolling a patient who is entered in a trial not listed on the trial website, the patient should be discussed with the central trial office. Patients may also be co-enrolled in observational studies e.g. additional imaging studies of the atherosclerotic plaque taken at the same time as the brain scan performed according to the ECST-2 protocol.

NON-RANDOMISED PATIENTS

An anonymised screening log will be kept of patients undergoing treatment for carotid stenosis by the trial investigators but not randomised at the participating centres. Centres will be encouraged to record screened patients using the web-based data collection system.

CONSENT

Written witnessed, informed consent will be obtained from all patients who will be provided with a written information sheet. A copy must be retained by the randomising centre.
Since we aim to determine the effect of trial interventions on cognitive function patients will be asked at randomisation to consent to continued follow up in the event of loss of capacity e.g. because of dementia, provided such continued follow up is not causing distress. In such cases, their representative will be asked to confirm that they are of the opinion that continued follow up in the trial will not cause them distress.

RANDOMISATION

A web-based randomisation system will be used accessible via the trial website (www.ecst2.com). Patients with either asymptomatic or symptomatic carotid stenosis who conform to the inclusion criteria will be randomised into the trial. The randomisation form will include entry of data to confirm a CAR score of <20% (see below for details of the CAR score and its calculation). Patients will be randomly allocated in a 1:1 ratio to be treated either by 1) immediate carotid revascularisation plus OMT or 2) by OMT alone (in the latter arm, revascularisation may be performed at a later stage if it becomes more clearly indicated e.g. because of TIA or stroke during follow up). Centres will be asked to pre-specify whether CEA or

CAS revascularisation is planned should the patient be allocated revascularisation. It is anticipated that the majority of revascularisation procedures will be endarterectomy.

The allocation will be balanced by minimisation on the following factors: recruitment centre, planned method of revascularisation (endarterectomy, stenting, angioplasty) and risk group (asymptomatic with stenosis ≥70%, asymptomatic with stenosis <70%, and CAR score. The minimisation incorporates a random component so that the treatment group that minimises imbalance is chosen with probability 0.85. Separate randomisation lists will be maintained according to whether endarterectomy or stenting is the pre-specified treatment.

INVESTIGATIONS BEFORE RANDOMISATION

Patients will be seen by the study neurologist or stroke physician prior to randomisation to confirm suitability for the study.

The following investigations will be required prior to randomisation:

1. Routine haematology (FBC, platelets)
2. Blood biochemistry (renal function, blood glucose, lipids)
3. Serum troponin
4. Electrocardiogram (ECG)
5. Imaging of both carotid bifurcations showing the severity of stenosis bilaterally
6. Brain MRI with vascular sequences (T2, FLAIR, gradient echo T2* and/or SWI, DWI/ADC). If MR is contra-indicated or not available within a reasonable time period for any reason, brain CT should be done instead.

Where appropriate facilities and permissions are available for storage of research tissue, additional blood samples will be taken for DNA, proteomics, markers of infection and inflammation, and biomarker analysis.

The baseline brain MRI is required to exclude other pathology, to identify existing infarcts and small vessel disease, and to provide a baseline reference against which any subsequent infarction or haemorrhage can be assessed. In exceptional cases where time pressure leads to trial centres experiencing problems performing an MRI before randomization, patients may be randomised using a CT to exclude other pathology and an MRI performed *after* randomisation so long as this is done within 14 days of randomization and before the scheduled time of revascularisation.

Preliminary work has identified extensive small vessel disease as a risk factor for surgery, while silent cerebral infarcts may increase the long-term risk of future stroke. Analysis in the central trial office will therefore be performed to determine whether baseline MRI improves prediction of risk and therefore selection of patients for early revascularisation, as well as for blinded analysis of rates of cerebral infarction and haemorrhage on follow up MRI.

ECST-2 will not specify the initial modality to be used to image the carotid bifurcation prior to patient selection because different units make use of various different non-invasive modalities to image the carotid bifurcation, including Duplex Ultrasound, CT angiography (CTA), and/or MR angiography (MRA). Digital Subtraction Angiography (DSA) is now rarely utilised except when the diagnosis is in doubt after initial non-invasive imaging, and will only be performed in patients in ECST-2 if clinically indicated. Ultrasound imaging of both carotid bifurcations will be required in all patients. Confirmation of the severity of the stenosis and the relevant vascular anatomy, including views of the arch, will be required from a second imaging investigation after initial screening. This confirmatory imaging should preferably be either MRA or CTA if the initial screening test has been ultrasound, rather than a repeat ultrasound. Where available, additional imaging of the carotid plaque, e.g. MR plaque imaging, 3D ultrasound imaging, and other measures of risk (e.g. emboli monitoring using transcranial Doppler) will be performed and the results analysed in the central trial office to refine prediction of risk. At the time of screening and randomisation, investigators will be required to determine as far as possible from the available non-invasive imaging (standard ultrasound, MRA or CTA) whether the plaque on the randomised side is smooth or ulcerated in order to calculate the CAR score.

Digital copies of the MRI or CT scans and the imaging of the carotid bifurcation will be sent to the Central Trial Office for central analysis together with copies of ECGs and the written reports of the imaging studies. Where more than one imaging modality has been used to image the brain or carotid bifurcations, copies of all the investigations will be sent to the Central Office. Carotid ultrasound data returned to the central office will include velocity data, a representative 2D longitudinal duplex section showing the largest carotid plaque area, and three 10 second videos of the carotid plaque, one visualized in a representative, longitudinal section by B-mode imaging only, one with B-mode and colour-Doppler enabled and the third 10 second video will be in cross section moving the transducer along the axis of the carotid artery from proximal CCA to distal ICA (2D cross-sectional sweep). Additional 3D acquisitions will be recorded at centres with appropriate equipment.

BASELINE DATA

Baseline data will be collected at randomisation using an electronic case record form and will include demographic data; existing medical risk factors; neurological symptoms including an assessment of disability using the modified Rankin Scale (see Appendix I); current antiplatelet and/or anticoagulant treatment, cholesterol lowering and hypotensive therapy and blood pressure recorded at the time of randomisation, together with copies of the images and reports of pre-randomisation brain and carotid imaging as detailed above. Blood will be taken to measure baseline serum lipids and blood glucose, preferably after fasting, together with a troponin level, if not available from previous samples within 2 weeks of randomisation. If only non-fasting measurements of serum lipids and blood glucose are available, a fasting measurement should be arranged if total cholesterol, LDL or blood glucose measurements are above target values.

CAROTID ARTERY RISK SCORE

The Carotid Artery Risk (CAR) score used at randomisation in this trial predicts the 5-year risk of ipsilateral stroke of patients with carotid stenosis. The algorithm used to calculate the CAR score is an adaption of the Carotid Stenosis Risk Prediction Tool, currently found on the website of the Stroke Prevention Research Unit at the University of Oxford. The latter program is based on the results of a Cox regression model and estimates the one-year and five-year risks of ipsilateral ischaemic stroke on medical treatment in patients with recently symptomatic carotid stenosis. The model was derived [3,4] on patients who had been randomised to medical treatment in the European Carotid Surgery Trial (ECST) [1,31] and was independently validated on the equivalent patient group in the NASCET trial.[4] The model showed good accuracy and calibration in the validation in NASCET and has since been used widely in routine clinical practice, both in its full web-based form and in the form of the risk tables derived from the model.[4] The web-based tool has been accessed over 12,000 times by clinicians who have entered patient data in order to calculate the predicted risk (current average >100 patients per week). The predictive values of the individual variables included in the model have also been reported.[32]

Our hypothesis is that the risk of stroke in patients treated medically will be halved on OMT compared to the rates seen in earlier trials. The carotid stenosis risk prediction tool mathematical model has therefore been recalibrated to allow for the effects of OMT compared to the regimes used for medical treatment in the original trials using additional data. It has also

been adapted to include asymptomatic stenosis and stenosis with no ipsilateral symptoms in the previous 180 days, assuming that these have a 5-year ipsilateral stroke risk of 5% or less.

Centres will be encouraged to screen all patients with carotid stenosis using the web-based randomisation system, which incorporates the CAR prediction tool. The program captures relevant baseline patient data and uses these to calculate the CAR score. The CAR score is used to confirm suitability for the trial and stratify the patients prior to treatment allocation according to their predicted 5-year risk of stroke. Patients are eligible for the study if they are CAR score of <20%. Investigators receive feedback on whether the patient is eligible for the trial. If the patient has a high CAR score the patient is excluded and the investigator will be informed of the high score with the recommendation that the patient should be considered for immediate revascularisation outside the trial. An anonymised log of the data used to screen individual patients will be retained whether or not they are subsequently randomised in ECST-2 to establish the proportion of patients with carotid stenosis ≥50% included and the characteristics of those excluded from the trial.

TREATMENT

Optimised Medical Therapy

OMT will be applied to both treatment groups starting immediately after randomisation. This will follow relevant national and/or European guidelines and will include:

1) Optimal antiplatelet therapy according to clinical practice at the centre, e.g. aspirin and dipyridamole combined or clopidogrel monotherapy. If the patient requires anticoagulation for any reason (e.g. atrial fibrillation), the patient should be treated with an appropriate anticoagulant according to the practice at the centre as an alternative to antiplatelet therapy.

2) Treatment to lower cholesterol, (e.g. a statin) in line with current guidelines. Cholesterol levels will be monitored during follow up and therapy adjusted to maintain a target total cholesterol <4.0mmol/L, and an LDL cholesterol level <2.0mmol/L (or >40% reduction in non-HDL cholesterol if greater) together with low cholesterol diet.

3) Treatment to lower blood pressure (BP), adjusted to maintain a target BP appropriate to the patient (e.g. 140/90 mmHg for a patient aged under 80 years if the BP is measured in the clinic or 135/85 mmHg for the same patient using home blood pressure monitoring). A higher threshold may be used in patients with contralateral carotid occlusion or those who develop side effects at target values.

4) Patients will also undergo targeted risk factor modification according to a strictly prescribed risk factor monitoring and remediation plan, including smoking cessation advice and/or

reduction of body weight if relevant. Patients smoking at the time of randomisation will be encouraged to join a smoking cessation and support program and documentary evidence of this returned to the trial office. Patients with diabetes mellitus will undergo optimization of glycaemic control.

Success at achieving risk factor control and treatment targets will be monitored. Investigators, patients and their general practitioner will receive written advice concerning treatment targets. The targets may be modified during the course of the trial by the trial steering committee if necessary to take account of revised national guidelines, new evidence or data from the interim analysis.

Revascularisation

In patients allocated immediate revascularisation, this should be performed as soon as possible and not more than 2 weeks after randomisation if the stenosis is symptomatic, and not more than 4 weeks after randomisation if the stenosis is asymptomatic. Investigators will be asked to specify a planned date for revascularisation within these time frames at the time of randomisation to ensure compliance with this requirement. In a patient where revascularisation cannot be performed within these timeframes for any reason, randomisation should be postponed until surgery can be performed within the timeframe.

Endarterectomy protocol

Endarterectomy is to be done as soon as possible after randomisation by a designated consultant surgeon who has been approved by the Credential Committee. It will be carried out using whichever procedures are standard at the individual centre, including the use of local or general anaesthesia, and shunts or patches as required by the operating surgeon. Standard or eversion endarterectomy may be performed. Details of medications, surgical techniques and perioperative complications will be collected.

The excised plaques from endarterectomies performed in the study will be collected where possible for histological analysis of plaque composition and correlation with investigations and clinical data, subject to appropriate local arrangements and licensing for tissue storage if required.

Stenting protocol

ECST2 will include patients in whom it is planned that carotid revascularisation will be performed by stenting, so long as the randomising clinician, supported by a multidisciplinary team,

considers that in the relevant patient CAS is preferable to CEA and has a low risk of procedural stroke equivalent to that of CEA in standard risk patients.

Where a patient is less suited for CEA and a centre offers CAS as an alternative, stenting will be carried out as soon as possible after randomisation using endovascular techniques by a designated interventional consultant who has been approved by the Credentialing Committee. The designated interventionist should use a CE marked dedicated carotid stent that he/she has experience with and is approved by the Credentialing Committee. CE marked dedicated carotid embolic protection devices should be used wherever the designated interventionist considers it safe to do so and is familiar with the device selected. Periprocedural data to include pharmacological regime and periprocedural complications will be recorded.

The following list provides details of clinical and anatomic features that may be associated with increased procedural risk for CAS and which should be considered as relative contra-indications to selecting CAS as the method of revascularisation in ECST-2. However, individual factors will not necessarily represent absolute contraindications for CAS in experienced units. Those features marked with an asterisk are absolute contraindications to CAS and exclude the patient from CAS as the choice of revascularisation within ECST-2. These features are not exclusions to CEA in ECST-2 so long as the patient fulfils the other inclusion criteria for the trial.

Anatomic:

- Complex/recurrent arch anatomy (e.g. type III arches)
- Conjoint brachiocephalic/ left CCA trunk (i.e. "bovine" configuration) for a left sided lesion
- Marked tortuosity of the CCA en route to the bifurcation lesion
- Angulation of the distal ICA (if filter-type embolic protection is proposed)
- Angulation at the ICA origin

Lesion-specific (and disease burden):

- Significant arch atheroma*****
- >Two-thirds circumferential calcification at the lesion site*****
- Globular exophytic plaque at the lesion, which may not respond to stent placement*

Clinical:

- Age >70 years in patients with symptomatic carotid stenosis
- Renal function (which may be adversely affected by use of iodinated contrast)

Co-morbidities that may preclude the use of a periprocedural dual antiplatelet regime (i.e. aspirin plus clopidogrel)*****

If any of the absolute contraindications are found after a patient has been randomised in ECST-2 and allocated revascularisation by CAS e.g. during pre-stenting angiography, stent deployment should be abandoned and the patient referred for CEA or optimal medical treatment, whichever is considered most appropriate. The patient should remain in ECST-2 and should continue to be followed up in the trial.

PREVENTION OF THROMBOSIS DURING SURGERY AND STENTING

Therapy to prevent thrombosis should be started at randomisation but in patients allocated revascularisation the regime may be altered according to standard practice in each centre to cover endarterectomy or stenting e.g. from single to combined antiplatelet therapy. This should be continued according to standard practice after the procedure (e.g. aspirin plus clopidogrel for 4-6 weeks after stenting) and should be reviewed at follow up after revascularisation. The other components of OMT (e.g. statin and antihypertensive medication) should be continued throughout the periprocedural period unless contraindicated.

FOLLOW UP

Patients will be followed up by a neurologist or stroke physician, or a clinician/research practitioner under their close supervision, within 48 hours after revascularisation and will have an ECG and cardiac biomarkers measured according to practice at the centre (preferably troponin) at the same time point. They will also be followed up at 30 days after revascularisation, at this time point they will have a carotid ultrasound to assess success of the procedure. In ICSS, the median delay from randomisation to CEA was 11 days. The first follow up in patients allocated OMT alone will therefore be done 6 weeks after randomisation to match the expected delay between randomisation and 30-day follow up after revascularisation. This delay will be adjusted if the trial shows that CEA is performed more rapidly. Patients allocated OMT will have the same cardiac biomarker (e.g. troponin) measured at the 6 week follow up visit. Thereafter, a follow up examination of the patient will be done 6 months after randomisation and then annually after randomisation. An additional follow up 3 months after randomisation will be done by telephone, as will a 6 monthly follow up between annual visits. Telephone contacts will collect data using a validated telephone follow up outcome measure. At the same time, a check will be made on the patients' adherence to risk factor control and advice given to the patient as appropriate. If a suspected stroke outcome event is identified between visits, patients should have an additional follow up appointment arranged with the neurologist or

stroke physician investigator to establish the cause of the event and consider whether additional treatment is required e.g. revascularisation in those allocated OMT alone. All 30-day post-procedural complications after revascularisation and other outcome events will be reported in detail to the central office. At each visit, levels of disability will be assessed using a structured interview to determine the modified Rankin Scale (appendix) and any outcome events notified to the Central Office. In patients with suspected or confirmed transient ischaemic attack (TIA) or stroke during follow up, an additional MRI brain scan will be done to confirm the diagnosis (unless contraindicated, when a CT will be done instead) together with an ultrasound or other re-examination of the carotid arteries. Copies of the images and reports will be returned to the trial office to assist with central adjudication and analysis. Copies of ECGs and results of cardiac biomarker measurements will be collected in patients suffering suspected or confirmed myocardial infarction.

Blood pressure (BP) will be recorded at each follow up visit. Patients will be informed of their target BP reading and encouraged to measure their BP at home, but BP may also be measured in the GPs surgery or at a clinic visit. Blood lipid and glucose measurements will be recorded at the one month/6 week visit and during annual follow up visits either from blood tests taken at the time of the visit or from blood tests performed by the patient's GP. If a non-fasting total cholesterol, LDL or blood glucose is above the target range, then fasting blood lipids and glucose should be arranged and medication adjusted as necessary.

A follow up duplex ultrasound of the carotid stenosis on the randomised and the contralateral side will be carried out at the one month after revascularisation in those patients randomised to immediate revascularisation and at 6 weeks after randomisation in those allocated OMT alone. Carotid ultrasound will then be done annually after randomisation in both arms of the study. The peak systolic velocities of the common carotid and the internal carotid arteries and the end diastolic velocity of the internal carotid artery will be recorded and reported to the central trial office.

Follow up brain MRI will be carried out at 2 years after randomisation and at 5 years after randomisation unless contra-indicated. If MR is contra-indicated or not available within a reasonable time period for any reason, brain CT should be done instead. For the safety analysis during the pilot study, an additional MRI may be performed at 30 days after revascularisation (or an equivalent period after randomisation in those allocated to delayed revascularisation), so long as the patient and the centre is willing to undertake the additional MRI.

Patients will have a simple test of cognitive function administered using the Montreal Cognitive Assessment (MoCA)[33] at randomisation, and then at the one month, 2-year and 5 year follow up visits.

As far as possible, visits, BP measurements and blood tests should take place within the time windows specified in the table below.

The duration of follow up will be a minimum of 5 years (or until termination of the trial if earlier). At the 5 year follow up, patients will be asked if they are willing to continue follow up, in which case annual follow up will continue up to a maximum of 10 years from randomisation.

Time Window Targets for Investigations and follow ups

Visit/Follow up/Investigation	**Target time window**
Baseline brain MRI	14 days before randomisation up to day of randomisation in symptomatic stenosis* 28 days before randomisation up to day of randomisation in asymptomatic stenosis* -
Initial baseline carotid imaging	120 days before randomisation up to the day of randomisation
Confirmatory second carotid imaging	14 days before randomisation up to day of randomisation
Baseline blood lipids and glucose, serum troponin levels	14 days before randomisation up to day of randomisation
Post procedure visit in revascularised patients	Day of treatment +48 hours ± 24 hours
One month follow up including MoCA.	Day of treatment + 30 days ± 7 days in Revascularisation patients Day of randomisation + 42 days ± 7days in OMT only patients†
One month carotid ultrasound in revascularised patients	Day of treatment + 30 days ± 7 days
One month MRI (optional)	Day of treatment + 30 days ± 7 days in revascularised patients Day of randomisation + 42 days ± 7days in OMT only patients*
3 month telephone follow up	Day of randomisation + 90 days ± 14days
6 month follow up	Day of randomisation + 180 days ± 14

	days
Annual follow up including MoCA, blood lipids and glucose, and carotid ultrasound, and MRI at 2 and 5 years	Day of randomisation + X years ± 1 month
Telephone follow ups between annual follow ups	Day of randomisation + X years + 6months ± 1 Month

*In exceptional cases, the baseline MRI may be performed up to 14 days after randomisation provided a CT has been done (see page 13).

†The time window in patients allocated OMT will be adjusted as necessary during the course of the trial to match the median delay between randomisation and one month follow up in the revascularisation arm.

COMPLIANCE

Treatment refusals and cross-overs will be minimised by careful informed consent. The effectiveness of the OMT regime will be monitored at follow up; GPs will be asked to monitor patients' blood pressure and cholesterol at regular intervals and these data will be collected at the scheduled trial follow up visits. We will aim for a rate of complete loss to follow up of less than 1%.

CROSSOVERS

Crossovers will be avoided unless clinically essential. Patient refusal of the treatment to which they are randomised will be minimised by careful consent. It is anticipated that early cross over will primarily occur in patients randomised to revascularisation in whom contraindications to intervention emerge after randomisation, so that they do not receive early revascularisation. Patients randomised to OMT alone should only receive revascularisation of the randomised artery if they have ipsilateral symptoms after randomisation which are attributed to the carotid stenosis and are considered to necessitate revascularisation. Patients requiring revascularisation because of new symptoms after allocation to OMT alone, as well as those requiring revascularisation of the contralateral, non-randomised carotid artery or needing a second carotid revascularisation procedure (e.g. because of symptomatic restenosis) may be re-treated with whichever method of revascularisation the local investigator considers most appropriate.

OUTCOME EVENTS

The following conditions will be reported as outcome events (see Appendix 1 for definitions):

- Stroke (with separate analysis of ischaemic, haemorrhagic, ipsilateral carotid, contralateral carotid, and posterior circulation stroke, and classification by impact on modified Rankin score)
- Cerebral infarction
- Intracranial haemorrhage (subarachnoid, intracerebral, subdural, extradural)
- Retinal infarction
- Transient ischaemic attack
- Amaurosis fugax (transient monocular blindness)
- Myocardial infarction
- New onset epileptic seizure
- Hyperperfusion syndrome
- Death (fatal stroke, fatal myocardial infarction, other vascular death, sudden death, other non-vascular death)
- Any hospitalisation for vascular disease
- Carotid revascularisation during follow up other than that allocated at randomisation
- Cranial nerve palsy attributed to revascularisation
- Haematoma caused by treatment requiring surgery, transfusion or prolonging hospital stay
- Other adverse events attributed to medical treatment or revascularisation
- Further revascularisation of the randomised artery after the initial attempt
- Decline in cognitive function
- Decline in functional status as assessed by an increase in the modified Rankin score (mRS)

In addition, measures will be reported relating to quality of life and health status, and health service use (e.g., length of stay in hospital, surgery, medications) and health service costs.

OUTCOME EVENT REPORTING AND AJUDICATION

Outcome events will be documented in detail by the investigating centre. Patients suffering stroke should have an MRI brain scan as soon as possible after the event. Centres are encouraged to perform MRI after all suspected neurological events, but CT should be used if MRI is contra-indicated or not available. A film or electronic copy of this, together with a film or electronic copy of the pre-randomisation scan will be submitted together with a report of the event. For MI, documentation of changes in cardiac biomarkers and copies of ECG recordings

should be returned to the trial office. The event report will include copies of discharge summaries; death certificates and post mortem results if relevant. Deaths of UK patients will be tracked by flagging patients against the UK Registry of Births and Deaths. Disability after stroke and cranial nerve palsy will be assessed 30 days and six months after treatment or onset, using the modified Rankin scale (see Appendix I). Duration of symptoms will be recorded and outcome events will be classified as disabling if the Rankin score is 3 or more.

Reports of outcome events will be censored after receipt at the central office to remove information concerning treatment allocation as far as practical, and then sent for adjudication as soon as sufficient information concerning the event has been received. Major outcome events will be adjudicated by two neurologists or cardiologists, depending on the reported event, at least one of whom will be independent of the trial. If the two physicians differ significantly in the classification of the event, the data will be sent to another independent adjudicator for their views. Major conflicts will be resolved by consensus or a majority view if consensus is not achieved. Additional information may be requested at any time by the central office or an adjudicating physician.

BLINDING

Because of the nature of the interventions being compared it is not practical to blind patients or clinicians to the treatment allocated. However, all follow up will be performed by neurologists or stroke physicians or staff under their close supervision rather than the surgeons or interventionists performing revascularisation. The central office staff, Chief Investigator and Steering Committee will all remain blinded to the cumulative event rate in the two arms until the interim analysis is complete. They will then remain blinded until the trial is completed, unless advised to the contrary by the Data Monitoring Committee. Follow up MRI scans will be analysed blind to treatment received, providing a non-biased comparison of outcome in the two groups.

OUTCOME MEASURES AND DATA ANALYSIS

The primary outcome measure for the main trial will be stroke in any territory at any time, or periprocedural death attributed to carotid revascularisation. The primary analyses will examine the following question: What is the difference in the long-term survival free of any stroke, or periprocedural death in patients with atherosclerotic carotid stenosis at lower risk for stroke after randomisation to a policy of carotid revascularisation with OMT compared to OMT alone?

Periprocedural death will be defined as death occurring within 30 days of carotid revascularisation.

Secondary analysis will compare the long-term rates of the following outcomes:

- Ipsilateral stroke, confirmed/probable TIA, MI or any hospitalisation for vascular disease during follow up
- Disabling stroke during follow up
- New cerebral infarction or parenchymal haemorrhage on follow up MRI
- Increase in white-matter changes on follow up MRI
- Revascularisation during follow-up
- Stenosis progression (defined as recurrent stenosis of the randomised artery after revascularisation, or progression in severity of stenosis in a non-revascularised artery)
- The combination of stenosis progression or revascularisation during follow-up
- Functional status as assessed by comparison of modified Rankin scale scores
- The cost-effectiveness of carotid endarterectomy with OMT compared to OMT alone
- Cognitive impairment or dementia during follow up reported by the investigator and measured by the Montreal Cognitive Assessment (MoCA)
- Decline in functional status as assessed by an increase in the modified Rankin score (mRS)
- Health related quality of life and economic costs

Secondary analysis will also examine the risk factors for stroke, cognitive impairment and the other main outcome events during long term follow up (including the risks related to age, sex, symptoms, baseline brain imaging, centre and technique). In centres performing the relevant additional investigations, secondary analyses will examine the relationship between the main outcome events and baseline measures of plaque instability as determined by MR plaque imaging, ultrasound plaque imaging, transcranial Doppler, DNA analysis and serum biomarkers.

The primary analysis will be by intention to treat using standard statistical tests by the trial statistician. The analyses will compare the treatment groups with respect to the length of time before treatment failure (i.e. occurrence of an outcome event) by means of the Mantel-Haenszel chi-squared test and Kaplan-Meier survival curves. A per-protocol analysis will be performed as an indicator of the actual treatment effect and will include only patients commencing or receiving the allocated treatment within 6 weeks of randomisation. In the per-protocol analysis, cross-overs to revascularisation without relevant symptoms within the first 6 weeks of randomisation, and patients in whom there are delays of more than 6 weeks in performing CEA

or CAS, will be excluded, while patients allocated OMT alone who receive carotid revascularisation more than 6 weeks after randomisation will be censored at the time of onset of the revascularisation procedure. All analyses will be adjusted for centre and predetermined risk factors and for type of revascularisation procedure and time to revascularisation procedure.

The analysis will also compare the primary outcome measure according to the adjusted 5-year CAR score at randomisation (dichotomised and as a continuous variable). Subgroup analyses will examine the influence of individual risk factors for outcome events. Subgroups of particular interest will be age (dichotomised at mean, and as a continuous variable), sex, diabetes, hypertension, severity of stenosis, contralateral stenosis or occlusion, type of most recent event, multiple symptoms, centre recruitment, and time from event to revascularisation. The results will also be analysed according to adherence to OMT targets.

The results of any data analysis presented to the Data Monitoring Committee will remain confidential to the trial statistician and Data Monitoring Committee members until such point as the Committee recommends unblinding of some or all of the data, or until completion or early discontinuation of the trial. Investigators and the Steering Committee will remain blind until such point.

MRI ANALYSIS

The primary outcome measure for the MRI-based analysis will be the combined 2-year rate after randomisation of cerebral infarction, cerebral haemorrhage, MI or procedural death as assessed by follow up MRI and screening for MI. The primary MRI analyses will examine the following question: What is the difference in the combined 2-year rate of cerebral infarction, cerebral haemorrhage, MI or periprocedural death after randomisation as assessed by follow up MRI and screening for MI?

The following secondary analyses will be performed:

- What is the rate of infarction in brain areas supplied by the randomised carotid artery?
- What is the total volume of infarction or haemorrhage in the two arms?
- Is cerebral infarction or haemorrhage or progression of white matter disease on MRI associated with cognitive decline measured by the Montreal Cognitive Assessment tool?
- Is progression of stenosis in the OMT arm or recurrent stenosis in the revascularisation arm associated with an increase in risk of subclinical cerebral infarction?

Standard stroke MRI sequences will be performed for the study including the following: T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) and gradient echo T2*-weighted imaging (or alternatively, susceptibility-weighted imaging [SWI]). 1.5 or 3.0 Tesla scanners may be used, so long as at each centre, the same field strength and the same imaging parameters are used for the baseline and follow up scans.

Copies of the brain imaging will be analysed at the Central Office to determine rates of silent cerebral infarction and other indexes of vascular disease e.g. progression of white matter disease. DWI will be used to identify acute cerebral ischaemia. The long-term accumulation of cerebral infarction will be assessed by follow-up fluid-attenuated inversion recovery (FLAIR) imaging. Gradient echo T2* imaging will be used to identify cerebral haemorrhage and cerebral microbleeds. The baseline and follow up images will be independently assessed by a neurologist and neuroradiologist blinded to treatment. Differences between the two observers will be resolved by consensus. Images will be assessed for any new brain lesions on follow up MRIs that were not present on the baseline MRI. A detailed definition of MRI outcome measures is provided in an Appendix.

SAMPLE SIZE

The planned sample size for the interim MRI-based analysis is 320 patients. We estimate that 12% of patients on OMT will have ischemic lesions after 2-years. This is based on a 2 year stroke incidence of 6% and the observation that ischemic lesions occur at roughly twice the rate of clinically obvious events. [24,25,29] This is in line with other studies: Fu *et al* studying the effect of statins on the progression of asymptomatic middle cerebral artery stenosis found 8 new ischaemic lesions on MRI in 103 untreated patients after 2 years, 3 of which were symptomatic.[29] In the CEA arm, 3% of patients in the CEA arm are likely to have strokes after 1 month and a further 6% will likely have new MRI lesions without clinically obvious symptoms [19] Thus, we anticipate that 9% of patients undergoing revascularisation will have new lesions by 1 month. We therefore calculate that the total rate (one month plus 2-year) of new cerebral infarction in patients receiving CEA will be 15%. Using a non-inferiority design, our sample size of 320 will have 80% power to show at a 5% significance level that the risk of MRI lesions at 2 years on OMT is not more than 7.5% higher than the risk in the CEA arm (equivalent to a risk ratio of 1.5).

We will also estimate that the rate of the combined outcome event of cerebral infarction, cerebral haemorrhage, MI or periprocedural death at 2 years. The 30 day MI rate in the CREST

trial was 2.3% for surgical patients.[20] The baseline characteristics of patients in ICSS would suggest a 2 year risk of MI slightly more than 2% using the Framingham model.[34] This is in line with what we have seen to date in ICSS (unpublished observations). Thus we estimate a total two year risk of MI of 4.5% in patients randomised to revascularisation and 2.1% in those randomised to OMT. The periprocedural death rate (unrelated to MI or stroke) in ICSS surgical patients was 0.1%. Thus we estimate that the rate of the combined outcome event will be 8% in the OMT arm alone (cerebral infarction plus MI) and 20% in the revascularisation arm (cerebral infarction plus MI plus periprocedural death). 160 patients in each arm of ECST-2 will give us a power of 85% to demonstrate this difference at a significance of p=0.05.

The planned sample size of the full trial is currently 2000. For sample size calculations of the full trial, we have assumed that the 5-year rate of the primary outcome event (any stroke plus periprocedural death) in the surgery arm of ECST-2 will be 9%, which is the rate in the CEA arm of ICSS, estimated from Kaplan Meier Curves, based on current follow up data. Given that the inclusion criteria for ECST-2 is a 5-year stroke risk of <20% according to the CAR score, we expect a range of risks within the inclusion criteria between 1 and 20% with an estimated average 5-year rate of stroke in the OMT alone arm of 8%. Given that we do not expect much difference between the 2 arms, the strength of the evidence we will produce will be determined by the width of the confidence intervals. The choice of sample size then depends on the how small a confidence interval is considered convincing. Our view is that given our current estimates of likely event rates, a total sample size of 2000 for the full trial is sufficient. To examine the difference between the two arms of ECST-2, we will estimate the difference between the two proportions. Given that the 5-year proportion of the primary outcome event in the surgical arm will be 0.09, then with a sample size of 1000 in each group, the width of the confidence interval will be ± 0.029 or 2.9 percentage points. If against our hypothesis, there is a marked difference favouring one arm, conventional power calculations estimate that with 2000 patients, we could detect meaningful differences with sufficient power e.g. a difference of 4% points (10% vs 6%) could be detected with 90% power.

Of necessity, when comparing revascularisation which carries an additional early risk of outcome events associated with an expected lower long-term risk against OMT alone, which will not have the additional early risk, any power calculation, such as those given above are a simplification of a complex situation where short term risks may be being traded off for long-term gains. One of the aims of the interim analysis is to provide information to determine if the actual event rates are consistent with the estimates used for the calculation of the total sample size and remain an appropriate basis for an equivalence comparison.

COST-EFFECTIVENESS ANALYSIS

We will undertake a detailed analysis of the cost and cost-effectiveness of carotid revascularization (either by CEA or CAS) with OMT versus OMT in patients with carotid stenosis at lower risk for stroke. Our analysis will conform to accepted economic evaluation methods.[35] We will estimate cost and cost-effectiveness during the 'within-trial' period (5 years/within-trial model) and also over the expected lifetime of the patient (lifetime/long-run model) – we anticipate that 85-90% study participants will still be alive at 5 years. Since we anticipate that the UK will recruit most patients to the trial, costs will be assessed from the perspective of the NHS and personal social services (PSS) in the UK, but we will collect relevant data from patients from other countries and will collect resource use data for all patients. Cost components collected during the trial and included in the analysis will consist of the detailed cost of: revascularisation procedures; OMT; imaging; thrombolysis; length of hospital stay by type of unit/ward (hyperacute stroke unit, acute stroke unit, general ward); outpatient visits by type of unit; physiotherapy, speech therapy, occupational therapy after discharge; primary care contacts; PSS contacts including home help, meals on wheels, and day centre visits; and any other prescribed medications. The volume of resource use for each cost component will be measured directly in the trial from patient records and using patient diaries. Patient records will be used to assess volume of secondary care use throughout the 5 year follow-up period. Patient diaries will be used to assess the volume of resource use for all types of contact during the first year only. We will compare the secondary care volumes from the patient records in the first year to the secondary care volumes in the patient diaries to assess the accuracy of the patient diaries. Definitive data on the volume of secondary care use will be taken from the patient records. Data on the volume of secondary care and PSS use will be taken from the patient diaries. Note this will be collected in the first year only. We will assume costs in the second half of the first year (to allow for higher use directly after randomisation) are replicated throughout years 1 to 5. Unit costs will be taken from standard published sources.

The cost-effectiveness measures in the within-trial model will be the incremental cost per change in long-term survival free of any stroke or periprocedural death (the primary outcome in the main trial), as well as the incremental cost per quality-adjusted life year (QALY) gained. Costs will be measured as described. QALYs will be calculated based on the health related quality of life (HRQL) and mortality data collected during the trial. HRQL will be measured according to the EQ-5D health questionnaire (www.euroqol.org), which we will collect at each follow-up point for each individual patient across the whole five year period. Given the perspective of the evaluation, EQ-5D scores will be converted into utilities using an EQ-5D social tariff computed using data from a representative sample of the UK population.[36] Patient-

specific utility profiles will be constructed assuming a straight line relation between each of the patients EQ-5D scores at each follow-up point. The QALYs experienced by each patient from baseline to 5 years will be calculated as the area underneath this profile. Multiple imputation by chained equations will be used to deal with missing EQ-5D and resource use values. Subsequent analyses of imputed data will include variance correction factors to account for additional variability introduced into parameter values as a result of the imputation process. Cost-effectiveness will be calculated as the mean cost difference carotid revascularization (either by CEA or CAS) with OMT versus OMT divided by the mean difference in outcomes (long-term survival free of any stroke, MI or periprocedural death /QALYs) to give the incremental cost-effectiveness ratio (ICER). Non-parametric methods for calculating confidence intervals around the ICER based on bootstrapped estimates of the mean cost and QALY differences will be used.[37] The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will show the probability that revascularization with OMT is cost-effective at 5 years for different values of the NHS' willingness to pay for an additional QALY. We will also subject the results to extensive deterministic (one-, two- and multi-way) sensitivity analysis. We will undertake cost-effectiveness analyses by patient sub-groups using pre-defined groups.

In the lifetime model cost-effectiveness will be calculated in terms of the incremental cost per QALY gained by carotid revascularization (either by CEA or CAS) with OMT versus OMT. A brief review of the NIHR HTA website (www.hta.ac.uk/project/htapubs.asp) and the NHS Economic Evaluation Database (NHS-EED, www.crd.york.ac.uk/) reveals that here have been few directly relevant previous analyses. Henriksson et al investigated the cost-effectiveness of carotid endarterectomy plus best medical management versus best medical management alone in patients with asymptomatic carotid artery stenosis.[37] The analysis, which took a Swedish societal perspective, was based mainly on data from the Asymptomatic Carotid Surgery Trial (ACST). Cost-effectiveness was measured in terms of the incremental cost per QALY gained over a 40 year time horizon. The analysis was based on a Markov model design. In a Markov structure, hypothetical individuals are in one of a set of mutually exclusive health states at each point in time. During intervals of equal length (referred to as Markov cycles), individuals can make a transition from one health state to another, with transitions being determined by transition probabilities. Each health state is associated with a cost and a health outcome. Costs and health outcomes from each Markov cycle are accumulated and summarized for the cohort at the end of the analysis. The Henriksson et al Markov model used four health states: 'no event'; 'post-non-disabling stroke'; 'post-disabling stroke'; and, 'dead', with costs, QALYs and transition probabilities for each state taken from ACST, supplemented with additional data from a national vascular database and other published sources. We will develop a de novo cost-effectiveness

model also using a similar Markov design that will be populated based on available evidence, including the data collected during the trial. Following decisions about model structure, a list of parameter estimates required for the model will be developed. The specific details of the data to be used to populate the model will be determined following the development of the structure and the systematic searches of the literature to identify existing models. We will undertake deterministic (one-, two- and multi-way) and probabilistic sensitivity analysis, the latter assuming appropriate distributions and parameter values.[38]

The analysis described above is subject to change following the interim analysis, up to which time we aim to collect data that can be used to plan the cost-effectiveness analysis in the main trial. Within this framework the objectives from the pilot study with regards the cost-effectiveness analysis are to identify: (1) the main NHS/PSS cost components that ought to be included in the main trial; (2) the best methods for collecting resource use data required for each of these cost components (e.g., patient diaries, patient records) and over what time period; (3) how best to collect EQ-5D data in the main trial; (4) potential sources that could be used to estimate residual life expectancy and other long term outcomes among patients.

PUBLICATION POLICY

Analysis of the results of ECST-2 will be prepared by the Central Office. A writing committee appointed by the Chief Investigator with advice from the Trial Steering Committee will prepare the main manuscripts. The writing committee will include representatives from the central office staff and the most active recruiting centres. Members of the writing committee will be expected to conform with the requirements for authorship and contribution published by the International Committee of Medical Journal Editors (www.icmje.org). A draft of any publications will be circulated to participating centres for comment prior to submission of the manuscript for publication on behalf of all the ECST-2 collaborators. The main publications from this trial will be published on behalf of the ECST-2 Investigators, who will be listed in the first main publication. Publications will acknowledge the main sources of sponsorship and funding for the research. The sponsors and funders of the research will have no role in data analysis, interpretation, or the writing of publications.

National co-ordinators who have taken on responsibility for organising the trial in their own countries may publish data obtained in those countries in national journals with the agreement of the Chairman of the Trial Steering Committee and the Chief Investigator after the main trial results have been published.

STEERING COMMITTEE

The Steering Committee (TSC) will consist of the Chief Investigator and individuals participating in and independent of the trial with experience in vascular neurology, cardiovascular disease, vascular surgery, vascular radiology, interventional neuroradiology, health economics, clinical trials and statistics, together with patient and carer representatives. Individual Country Coordinators from the most active centres will be represented on the committee. The TSC will have an independent Chairman and will oversee the overall management of the trial.

DATA MONITORING COMMITTEE

The safety aspects of the trial will be overseen by an independent Data Monitoring Committee with expertise in neurology, clinical trials, medical statistics, vascular surgery and clinical pharmacology. The progress of the study will be assessed at regular intervals determined by the Data Monitoring Committee. During the period of recruitment to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to treatment) will be provided, in strict confidence, to the Data Monitoring Committee by the trial statistician, along with any other analyses that the Committee may request. In the light of these analyses, the Data Monitoring Committee will advise the chairman of the Steering Committee if, in their view, the randomised comparisons in ECST-2 have provided **both** (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, **and** (ii) evidence that might reasonably be expected to materially influence patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

REPORTING OF POOR OUTCOMES AT INDIVIDUAL CENTRES

If the local investigator or other member of the team, at a trial centre has concern about the outcome of their trial procedures, they should inform the trial office, which will organise a

blinded assessment of the relevant outcome events. This will be submitted by the central office to the chairman of the Data Monitoring Committee who may recommend further action, such as suspending randomisation at the centre. Similarly, the database manager at the trial office will monitor outcome events and if there are two consecutive deaths or three consecutive major events at a single centre within 30 days of treatment in the same arm of the study, then assessment of the events will be triggered. A cumulative major event or death rate of 10% or more over 20 cases would also trigger careful assessment of the relevant outcome events.

TRIAL ORGANISATION

The study will be organised on behalf of the collaborators by the Central Trial Office, currently located at the UCL Institute of Neurology in London. The office will be responsible for protocol design, data collection and management, and analysis of the results in consultation with the Steering and Data Monitoring Committees, but will consult with the collaborators at an annual meeting and at other times as necessary. Communication with investigators will also take place via a regular newsletter and the trial website.

SPONSORSHIP AND INDEMNITY

ECST-2 is an academic trial performed as a collaborative effort for the benefit of patients, and is not performed for, or on behalf of an industry sponsor. University College London (UCL) will take on the role of trial sponsor. UCL will hold insurance against claims from participants for injury caused by their participation in ECST-2. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if ECST-2 is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Hospitals selected to participate in ECST-2 must provide clinical negligence insurance cover for harm caused by their employees. A copy of the relevant insurance policy or summary can be provided on request. UCL may delegate sponsorship responsibilities to another organisation e.g. within another jurisdiction, subject to appropriate contracts.

RISKS OF THE TRIAL

The trial compares two existing forms of treatment currently used in many hospitals. Hence, the trial is not a test of a new treatment with unknown hazards. It is expected that some patients may be harmed inadvertently as a result of revascularisation in the trial and similarly OMT is not expected to prevent all vascular events. Indeed, the determination of the rate of these outcome events is a major aim of the trial. However, we believe that all patients in the trial should benefit from inclusion in the trial because of the attention to their care defined by the protocol. The trial protocol does not subject patients to hazards that the patient would not have encountered if they had received the trial treatments outside the context of the trial in routine practice. The UK Government Medicines and Healthcare products Regulatory Agency (MHRA) has confirmed that ECST-2 is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC.

WEBSITE

The trial website www.ecst2.com will contain updated information about the trial together with downloadable copies of the protocol, newsletters and contact information. The names of the collaborating centres will be included on the website. The main website address pages will be accessible to the public, patients and collaborators alike without a password. The website will include links to a password protected secure website with facilities for on-line screening, patient randomisation and trial data collection forms currently managed by Sealed Envelope. This website will maintain a database of all entries on the website, which will only be accessible to a limited number of trial staff trained in data protection.

REFERENCES

1. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-1387

2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in-patients with symptomatic, moderate or severe stenosis. NEJM 1998;339:1415-1425

3. Rothwell PM, Warlow CP on behalf of the European Carotid Surgery Trialists Collaborative Group. Prediction of benefit from carotid endarterectomy in individual patients: a risk modelling study. Lancet 1999;353:2105-2110

4. Rothwell PM, Mehta Z, Howard SC, et al. From subgroups to individuals: general principles and the example of carotid endarterectomy. Lancet 2005;365:256-265

5. Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010;363:1491-1502

6. McPhee JT, Hill JS, Ciocca RG, et al. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. J Vasc Surg 2007;46:1112-1118

7. Carotid Interventions Audit (CIA) Steering Group. UK carotid endarterectomy audit Round 4 public report. Royal College of Physicians Clinical Standards department. London, UK. August 2012

8. Gladstone DJ, Sahlas DJ. Should people with asymptomatic carotid artery stenosis undergo endarterectomy for primary stroke prevention? JAMC 2004;171:726-727

9. The Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo controlled trial. Lancet 2002;360:7-22

10. Sillesen H, Amarenco P, Hennerici MG et al. Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis. Stroke 2008;39:3297-3302

11. Milionis HJ, Giannopoulos S, Kosmidou M et al. Statin therapy after first stroke reduces 10-year stroke recurrence and improves survival. Neurology 2009;72:1816-1822

12. Marquardt L, Geraghty OC; Mehta Z, Rothwell PM. Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Treatment: A Prospective, Population-Based Study. Stroke 2010;41:e11-e17

13. Abbott AL. Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis: Results of a Systematic Review and Analysis. Stroke 2009;40:e573-e583

14. Rerkasem K, Rothwell PM. Temporal Trends in the Risks of Stroke and Death due to Endarterectomy for Symptomatic Carotid Stenosis: An updated Systematic Review. Eur J Endovasc Surg. 2009;37;504-511.

15.Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;**355**:1660-71.

16. Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;**368**:1239-47.

17. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;**7**:893-902.

18. Mas JL, Trinquart L, Leys D, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008;**7**:885-92.

19. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 375(9719):985-997.

20. Brott TG, Hobson RW II, Howard G, et al. Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis. NEJM 2010; 363: 11-23

21. Bonati LH, Dobson J, Algra A, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of pooled individual patient data. The Lancet 2010;376:1062–73.

22. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. New Engl J Med. 2007;357;1821-1828.

23. Cheung N, Mosley T, Islam A, et al. Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study. Brain 2010: 133; 1987-1993.

24. Coutts SB, Hill MD, Simon JE, et al. Silent ischemia in minor stroke and TIA patients identified on MR imaging. Neurology 2005: 65; 513-517.

25. Kang DW, Lattimore SU, Latour LL, Warach S. Silent ischemic lesion recurrence on magnetic resonance imaging predicts subsequent clinical vascular events . Arch Neurol. 2006: 63: 1730-1733.

26. Schnaudigel S, Groschel K, Pilgram SM, Kastrup A. New Brain Lesions After Carotid Stenting Versus Carotid Endarterectomy: A Systematic Review of the Literature. Stroke 2008;39:1911-1919.

27. Canyigit M, Arat A, Cil BE et al. Distal embolization after stenting of the vertebral artery: diffusion-weighted magnetic resonance imaging findings. Cardiovasc Intervent Radiol. 2007:30;189-195.
28. Bonati LH, Jongen LM, Haller S, et al., New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS), Lancet Neurol 2009;9:353-362.
29. Fu JH, Mok V, Lam W, et al. Effects of statins on progression of subclinical brain infarct. Cerebrovascular disease 2007: 30; 51-56.
30. Vermeer SE, Prins ND, den HeijerT et al. Silent brain infarcts and the risk of dementia and cognitive decline. New Engl. J. Med. 2003 :348; 1215-1222.
31. Rothwell PM, Gutnikov SA, Warlow CP for the ECST investigators: Re-analysis of the final results of the European Carotid Surgery Trial. Stroke 2003;34:514-523
32. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM for the Carotid Endarterectomy Trialists' Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and the timing of surgery. Lancet 2004;363:915-24
33.Pendlebury ST,Cuthbertson FC, Welch SJV, et al. Underestimation of Cognitive Impairment by Mini-Mental State Examination Versus the Montreal Cognitive Assessment in Patients With Transient Ischemic Attack and Stroke A Population-Based Study. Stroke 2010;41;1290-1293.
34 Wilson PWF, D'Agostino RB, Levy D, et al. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation* 1998;97:1837-1847.
35. Guide to the methods of technology appraisal. NICE, June 2008.
36. Dolan P. Modelling valuations for EuroQol health states. Medical Care 1997;35:1095-108.
37. Henriksson M., Lundgren F., Carlsson P. Cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis. *Br J Surg* 2008;95:714-20.
38. Briggs AH, Sculpher M, Claxton K. Decision modelling for health economic evaluation. OUP, Oxford, 2006

APPENDIX I

DEFINITIONS OF OUTCOME EVENTS & OTHER MEASURES:

MAIN OUTCOME EVENTS

- **Transient ischaemic attack (TIA):** An acute disturbance of focal neurological function with symptoms lasting less than 24 hours attributed to cerebrovascular disease. If imaging at the time shows evidence of relevant acute ischaemia or infarction, the event will be classified as confirmed TIA. In the absence of imaging confirmation, events will be classified as probable TIA if they satisfy the following criteria: 1. The patient must have had a documented sudden onset focal neurological deficit, either observed or the symptoms recorded by a doctor in the patient's medical record in sufficient detail to be certain about their nature. 2. The symptoms must have been typical, such as transient blindness on one side, dysphasic speech deficit or transient weakness on one side without a march of symptoms. Isolated brain stem symptoms e.g. vertigo, dizziness or diplopia will not be classified as probable TIA. In cases where the adjudication committee considers it appropriate, events may be classified as possible TIA.

- **Transient monocular blindness (Amaurosis fugax):** Acute total or partial loss of vision in one eye with recovery within 24 hours attributed to vascular disease. This will be included as a variety of TIA.

- **Stroke:** An acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance. It must be established whether the cause is infarction or haemorrhage (intracerebral or subarachnoid). Visual loss resulting from embolic or haemodynamic retinal ischaemia with symptoms or signs lasting more than 24 hours will be included within the category of stroke. Subdural haemorrhage and cerebral haemorrhage secondary to trauma will not be classified as stroke. Stroke will be classified as fatal stroke if the patient dies within 30 days of onset of the stroke and the death is attributed to the consequences of the stroke.

- **Myocardial Infarction:** The trial will use the Universal definition of Myocardial Infarction (MI).[1] Thus to be counted as an MI an event will have to fulfil one of the following three criteria:
  1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
     - Symptoms of ischaemia;
     - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
     - Development of pathological Q waves in the ECG
     - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  2. Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of thresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
  3. Pathological findings of acute myocardial infarction.

- **Cranial Nerve Palsy:** lower motor neurone weakness or sensory impairment in the distribution of one of the cranial nerves attributed to carotid revascularisation.

- **Haematoma:** bleeding attributed to carotid revascularisation requiring new surgery, transfusion or prolonging hospital stay.

- **Disabling Outcome Events:** disability after stroke and cranial nerve palsy will be assessed using the modified Rankin scale (defined below). Outcome events will be classified as disabling if the Rankin score is increased as a result of the event to 3 or greater at 30 days after onset. The modified Rankin scale will be recorded at one and six months after treatment and then at annual and additional follow ups. Investigators will be asked to estimate the Rankin scale score at one month after onset of new stroke if the patient has not been seen one month after onset.

- **Recovered strokes:** in patients who make a full recovery from stroke or other outcome

[1] Universal Definition of Myocardial Infarction. Kristian Thygesen, Joseph S. Alpert, Harvey D. White, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. *Circulation* 2007;116:2634-2653

events, the duration from onset to full recovery will be recorded in days.

- **Cognitive decline:** We will use the Montreal Cognitive assessment (MoCA) at randomisation, one month and 2 and 5 year follow up to examine if there is any difference between treatments in terms of cognitive decline and determine if silent cerebral ischaemia worsens cognitive decline. There is evidence that MoCA is more sensitive to cognitive abnormalities after TIA and stroke than the Mini Mental State Exam.[2]

IMAGING MEASURES

- **Cerebral infarction on MRI**: Any new hyperintense lesion on the fluid attenuated inversion recovery (FLAIR) sequence seen on the 2-year follow-up scan that was not present on the baseline scan, and that is consistent with the diagnosis of ischaemic infarction.

  The number, volume and location of ischaemic lesions will be assessed. Lesions will be considered separate if there is no continuity between them on the same and adjacent slices. Volume of separate lesions will be calculated by multiplying lesion diameters in 3 perpendicular axes and dividing the obtained volume in millilitres by 2.[3] Lesions will be assigned to the following vascular territories, according to published templates[4]: the carotid circulation (including anterior cerebral artery [ACA] and middle cerebral artery [MCA]), ipsilateral and contralateral to the side of the randomised artery; and the vertebrobasilar circulation (including both vertebral arteries, the basilar artery, cerebellar arteries, and both posterior cerebral arteries [PCAs]) will be discerned. Location will be further divided superficial brain areas (including cortex and subjacent white matter) supplied by leptomeningeal branches of the ACA, MCA, and PCA (also known as superficial or pial arteries) and deep brain areas supplied by perforating arteries. Vascular border zones will be defined as the area between ACA and MCA, between MCA and PCA, and between ACA, MCA, and PCA territories, as well as the area between territories supplied by leptomeningeal branches and perforating branches of the ACA, MCA, or PCA.

---

[2] Mini-Mental State Examination Versus the Montreal Cognitive Assessment in Patients With Transient Ischemic Attack and Stroke A Population-Based Study. Stroke 2010;41;1290-1293

[3] Pantano P, Caramia F, Bozzao L, Dieler C, von Kummer R. Delayed increase in infarct volume after cerebral ischemia: correlations with thrombolytic treatment and clinical outcome. *Stroke*. 1999;30:502–507

4 Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territo¬ries of the human brain. In: Bogousslavsky J, Caplan LR, eds. *Stroke Syndromes*. 2nd ed. Cambridge, United Kingdom: Cambridge University Press; 2001:375–404.

- **Cerebral haemorrhage on MRI**: Any new hypointense lesion on the T2* sequence or on SWI seen on the 2-year follow-up scan that was not present on the baseline scan, and that is consistent with the diagnosis of intracerebral haemorrhage. The number, volume and location of haemorrhagic lesions will be assessed in the same way as ischaemic lesions. In addition, haemorrhagic lesions will be classified as "microbleeds" or "macrobleeds". Microbleeds are defined as round areas of decreased T2* or SWI signal in the brain parenchyma of ≤10 mm diameter, that are not explained by other causes such as blood vessels (in the subarachnoid space) or calcifications of the basal ganglia. Microbleeds will be further classified as definite or possible, and their location as lobar, deep, and infratentorial, according to the previously published Microbleed Anatomical Rating Scale (MARS)[5].

- **Cerebral white matter changes** will be assessed on FLAIR images of the baseline and the 2-year follow-up scan using the semi-quantitative Age-Related White Matter Changes scale (ARWMC)[6].

- **Stenosis progression:** The degree of stenosis of the carotid artery on the randomised side and on the contralateral side at baseline and during follow-up will be determined in the central trial office based on the peak systolic velocities of the common carotid and the internal carotid arteries and the end diastolic velocity of the internal carotid artery obtained by duplex ultrasound. Degree of stenosis will be determined on the basis of predefined, standardised flow velocity criteria, which equate well with the severity of carotid stenosis measured on catheter angiography with the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[7]. The severity of stenosis seen on carotid angiography (MRA, CTA, or DSA) done in addition to ultrasound at the discretion of the treating physician, e.g. for recurrent symptoms, will also be measured according to the NASCET method.

  Severe recurrent stenosis after revascularisation will be defined as any severe stenosis (70-99% lumen diameter reduction) or occlusion of the carotid artery on the randomised side at any time after the initial procedure. Progression of stenosis in the OMT arm will be defined

---

5 The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jäger HR, Werring DJ. *Neurology*. 2009;73:1759-66

6 Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322

7 McCabe DJ, Pereira AC, Clifton A, Bland JM, Brown MM. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Stroke* 2005;36:281–86

as an increase in severity of stenosis to a degree of 70-79% or 80-95% luminal narrowing, near-occlusion (96-99% luminal narrowing) or complete occlusion from any lower degree of stenosis at any time after randomisation.

FOCUSED ASSESSMENT INTERVIEW FOR THE MODIFIED RANKIN SCALE

ECST-2 will use the Rankin Focused Assessment to assess the modified Rankin scale (mRS-SI). The Rankin Focused Assessment takes 3 to 5 minutes to apply and provides clear, operationalised criteria to distinguish the 7 assignable global disability levels of the Rankin Scale.[8] The purpose of the focused interview is to assign patients a mRS grade in a systematic way. The interview consists of five sections which correspond to the levels of disability on the traditional mRS. Information can be obtained from the patient or a relative/carer or from medical records. Investigators will be provided with instructions how to apply the Focused Assessment and complete the rating form. The Assessment provides specific questions to determine the patient's Rankin grade. After completing the Assessment with the patient or their carer, the overall rating is the worst disability category indicated by their answers. Investigators will write the grade on the follow up forms and send a copy of the rating form to the Central Trials Office.

[8] Saver JL, Filip B, Hamilton S, Yanes A, Craig S, Cho M et al. Improving the Reliability of Stroke Disability Grading in Clinical Trials and Clinical Practice: The Rankin Focused Assessment (RFA). *Stroke* 2010;41:992-995

APPENDIX II

Contact details for Enquiries and the Central Trial Office staff will be listed on the trial website at www.ecst2.com together with a list of enrolled centres and current trial committee members.