The Second European Carotid Surgery Trial (ECST-2)

A guide to patient screening, randomisation and follow up

European Carotid Surgery Trial – 2 (ECST-2)

The following pack has been put together to help facilitate the screening, randomisation and follow up of patients with carotid artery stenosis, whom may be suitable for inclusion into this trial.

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ECST-2 – Brief Summary

The 2nd European Carotid Surgery Trial (ECST-2) will investigate the hypothesis that in patients with atherosclerotic symptomatic or asymptomatic carotid artery stenosis, who are at low and intermediate risk for stroke, medical treatment adjusted to achieve guideline targets (optimised medical treatment, or OMT) will avoid the need for carotid surgery. ECST-2 will screen patients with symptomatic or asymptomatic carotid stenosis on-line using clinical and imaging characteristics to calculate a 5-year Carotid Artery Risk (CAR) score, which will stratify patients according to their likely risk of future stroke treated medically. Patients at high risk of stroke recurrence will not be included, but those at lower risk will be randomly allocated in equal proportions to be treated by 1) immediate carotid endarterectomy with optimised medical treatment or 2) optimised medical treatment alone. In the latter arm, endarterectomy may be performed at a later stage if it becomes more clearly indicated e.g. because of transient ischaemic attack during follow up. OMT in both arms will include antiplatelet therapy, high-dose statin treatment adjusted to achieve a target total cholesterol level and antihypertensive treatment with a target blood pressure. An interim analysis using MRI to determine rates of cerebral infarction and haemorrhage will be performed, with long-term follow up to compare clinical outcome events.

1. Patient Screening

All patients with a carotid artery stenosis of >50% should be screened for eligibility using the online screening tool on the ECST-2 website (www.ecst2.com). Once you have entered the patient details the website keeps a record of all patients as a 'Screening Log' regardless of whether they are subsequently randomised in the trial. Each patient will be given an individual 'Screening Number' and you should make a note of this. The screening process will record the following inclusion and exclusion criteria and if the patient is otherwise eligible then you can proceed to randomisation. From this we can determine what proportion of symptomatic patients are in general eligible for the trial even if they are not randomised. Screening needs to be done before a decision to operate is made. Patients can be screened on the initial carotid artery imaging e.g. carotid ultrasound or CTA.

Inclusion Criteria

- Patients must be over the age of 18 with atherosclerotic carotid stenosis equivalent to at least 50% measured using the NASCET method
- Patient is medically and neurologically stable and suitable for CEA
- Patients with a carotid artery risk (CAR) score indicating a low or intermediate 5 year ipsilateral stroke risk. This may include patients with asymptomatic or symptomatic stenosis associated with features (e.g. delayed presentation) indicating intermediate or lower risk, as confirmed by the online calculation of the CAR score
- Clinicians are uncertain about which treatment modality is best for the individual patient
- Patient or appropriate representative 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 >15% 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.

2. Imaging requirements

All potentially eligible patients need to have at least two modalities of carotid imaging, with concordant degree of stenosis. The modalities can include ultrasound and MRA, MRA and CTA or CTA and ultrasound. All patients who will be randomised also need to have had a baseline brain MRI, or CT brain if MR is contraindicated.

Patients need to be discussed on an individual basis between stroke physician/neurologist, radiologist and vascular surgeon (and/or interventional neuroradiologist) at a multidisciplinary team meetings or equivalent, to determine eligibility for the trial. A potential date for revascularisation should be identified (to be performed within 2 weeks of randomisation if symptomatic and within 4 weeks if asymptomatic).

3. Consent and randomisation

If a patient meets the inclusion criteria for recruitment to ECST-2 and they have had the appropriate baseline imaging then the attending neurologist or stroke physician, delegated representative or research practitioner/nurse should obtain informed consent. At this stage the trial should be explained carefully and an information sheet given to the patient. Allow the opportunity for any questions to be asked. Once

consent is obtained you will be able to log in to Sealed Envelope again and access the screening information via the allocated Patient Screening Number. You can then continue to randomise the patient and enter the data into the baseline form.

Consensus among researchers and clinicians has deemed it reasonable to complete a paper randomisation form initially before transcribing answers to the online forms. These paper forms are available for you if you wish to use them. The completed paper forms should then be stored in the site files for audit purposes, site monitoring visits and backup data.

Randomisation will be completed via an online randomisation form (www.ecst2.com). Once you have completed the patient details on the online randomisation form, and pressed the button to randomise, you will be presented with the randomisation result. Please print this screen shot also and store in the site file. Patients will be randomised to ***'Immediate carotid endarterectomy with optimised medical therapy'*** or ***'optimised medical therapy alone'***. If you are told that the patient is not suitable for randomisation because they are in the 'higher' risk group based on the Carotid Artery Risk Score, please consider revascularisation or optimal medical therapy outside of the trial.

4. At the randomisation visit:

The following investigations will are required to have taken place either before or at the randomisation visit:

- Routine haematology including FBC, platelets, WCC and RDW
- Blood biochemistry (renal function, fasting blood sugar, fasting lipid profile)
- Troponin
- DNA and proteomics analysis
- Electrocardiogram (ECG)
- Imaging of both carotid bifurcations showing the severity of stenosis bilaterally with **two** imaging modalities e.g. carotid Doppler ultrasound and CT angiogram or MR angiogram
- Brain MRI (T2, FLAIR, GRE, DWI and ADC) and MRA carotids. If done at your centre, specialised plaque imaging is also required before randomisation. If MRI is contra-indicated or not available within a reasonable time period for any reason, brain CT should be done instead
- Rankin Focussed Assessment (RFA), Montreal Cognitive Assessment (MoCA) and EQ5D should also be completed with the patient.

DNA samples should be sent to the Central Trial Office in the blue Royal Mail boxes provided.
You will be required to send copies of **ALL** imaging to the Central Trials Office.
You will also be required to send a copy of the ECG and 'Personal Data and NOK' form to the Trial Office. The EQ5D answers and blood results need to be entered online as part of the Baseline Forms.

5. After randomisation

For patients randomised to either ***'Immediate carotid endarterectomy with optimised medical therapy'*** or ***'optimised medical therapy alone'*** please prescribe antiplatelet therapy and adjust medication to maintain cholesterol and BP below target:

- Antiplatelet therapy e.g. aspirin and dipyridamole, or clopidogrel
- Cholesterol-lowering medication (target cholesterol <4.0mmol/L)
- Target blood pressure 135/85mmHg or less

For patients undergoing immediate endarterectomy please liaise with the vascular surgeons as they may not want optimal antiplatelets started until after surgery.

Give advice regarding other risk factors and refer to the appropriate agencies as required e.g. smoking cessation clinics and dietician.

Patients randomised to ***'Immediate carotid endarterectomy with optimised medical treatment'*** should undergo carotid endarterectomy (CEA) as soon as medically possible after randomisation. Details of the procedure, medications, surgical techniques and perioperative complications will need to be collected on the technical data forms and submitted to the trial centre.

At this point a letter should be sent to the patient's GP informing them about the patient's participation in the trial, randomisation outcome and what treatment the patient has or will receive. On discharge, these details should also be included in the patient's discharge summary.

6. Follow up

If the patient has been allocated ***'Immediate carotid endarterectomy with optimised medical treatment'*** they should be scheduled to have a carotid endarterectomy or carotid artery stenting within 2 weeks of randomisation if symptomatic and 4 weeks if asymptomatic. A 'Surgical/Stenting Technical Form' needs to be completed by the operating surgeon at the time or shortly after the operation. In this form we ask for details of the procedure including type of anaesthetic used, type of surgery/stenting performed and which ward the patient went to after revascularisation.

Between **24-48 hours** the patient should be assessed and have a repeat ECG and troponin (or other cardiac biomarker) performed. At this point you are required to complete the '48 hour follow up data collection form' which has questions regarding ICU stay, medications used before, during and after the procedure, and the incidence of any perioperative or postoperative complications.

Patients who are allocated to 'Optimised medical therapy (OMT) alone' do not need to be assessed at 48 hours and you will not need to collect a surgical/stenting technical form, as they will not have had a revascularisation procedure.

The next point of follow up for all patients is at **4-6 weeks** (30 days after revascularisation or 6 weeks for patients allocated to OMT alone). We want these times to be a similar time after randomisation in each arm, so the target first follow up date for OMT patients may be changed during the course of the trial. At 4-6 weeks patients will be reviewed at the outpatient clinic (or in hospital if they have not yet been discharged). At this point they will undergo a clinical assessment by a Neurologist or Stroke Physician. They need to have a repeat Rankin Focussed Assessment (RFA), MoCA and EQ5D performed and a repeat ultrasound of the carotids and MRI brain/MRA carotids should be organised for the same week. As with the baseline visit, all imaging needs to be sent to the Central Trial Office and a copy of the MoCA should also be sent. The Follow up form and EQ5D need to be entered online also. At this visit it is essential to optimise medical treatment and risk factor control. Patients randomised to 'OMT alone' also require having an ECG and troponin performed at this follow up appointment. Lipids and LFTs should be checked in any patient who has recently commenced a statin or in whom the statin dose was altered.

Research practitioners or clinical fellows are asked to telephone the patients at **3 months** post-randomisation and complete the Telephone follow up form.

At **6 months** patients will come back to clinic for a clinical assessment and medication and risk factor review. An EQ5D and Rankin Focussed Assessment (RFA)is also required at this visit.

Patients will be seen annually around the anniversary of their randomisation for at least 5 years. At **1, 3 and 4 years** the patient will be seen in clinic for a clinical assessment and medications review. EQ5D and carotid ultrasound should be repeated. At **year 2 and 5**, the patient will again be reviewed in clinic. At this time it is essential for a repeat MRI brain and MRA carotids and a MoCA, as well as EQ5D and carotid ultrasound. As with every follow up the patient should be assessed clinically and the physician should review their medication and vascular risk factors and complete a Rankin Focussed Assessment (RFA).

Practitioners are also required to contact the patients for a telephone follow up at 6 month intervals during the 1-5 year follow up.

7. Major event reporting

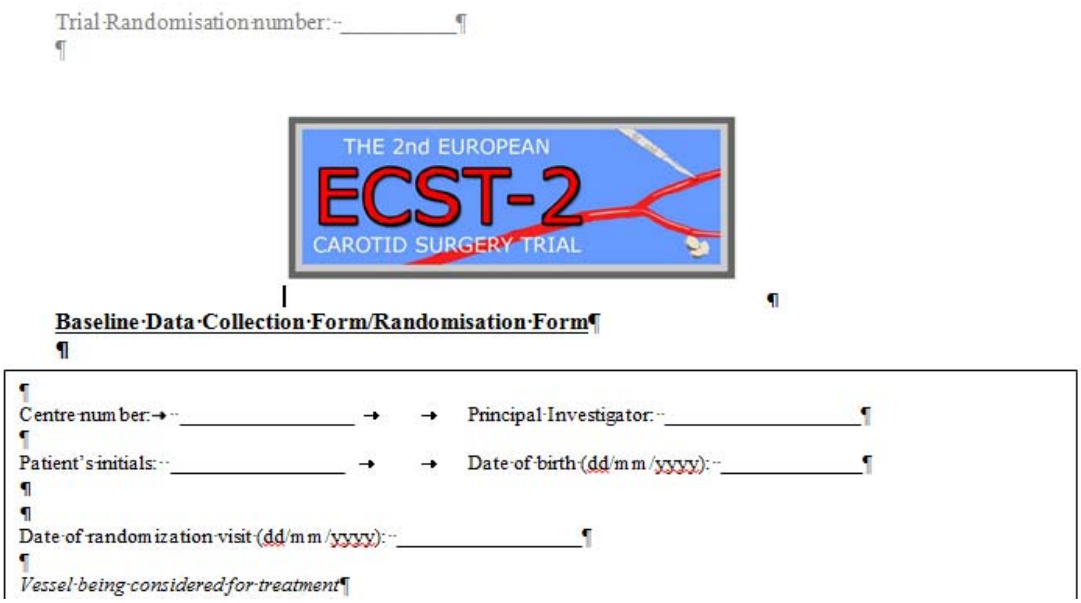
You will be required to complete Event forms if the patient has a major event. These include stroke/TIA, MI or death. If the patient has a stroke/TIA or a MI, which is fatal, you will need to fill out both the stroke/TIA or MI form and the Death form. In the follow up forms we do ask for information on hospitalisations or other illnesses, but these do not need to be reported as a serious adverse event (SAE). If patients have a stroke or TIA during follow up they will need to have a MRI brain (or CT brain if MR contraindicated). If patients have a MI during follow up then please arrange for them to have an ECG and troponin. As per protocol, all imaging and copies of ECGs must be sent to the trial central office and appropriate forms completed online (www.ecst2.com).

8. Cross overs

If a patient 'crosses over' please complete the cross over form. Cross overs should be avoided as far as possible by careful informed consent and ensuring that patients know that if they consent to the trial, they need to stick to the allocated treatment (unless some new event occurs). However, any patient who crosses over should continue to be followed up in the trial because the results of the trial will be analysed by 'intention to treat'.

Please ensure that a surgical/stenting technical form is completed for any carotid revascularisation procedure (endarterectomy, stenting or angioplasty) occurring at any time after randomisation, irrespective of whether it is for the randomised artery or the contralateral artery. **Patients should have an additional follow up performed 30 days after all revascularisation procedures.**

Where to find the trial documents



Trial Randomisation number: _____

THE 2nd EUROPEAN ECST-2 CAROTID SURGERY TRIAL

Baseline Data Collection Form/Randomisation Form

Centre number: _____ Principal Investigator: _____

Patient's initials: _____ Date of birth (dd/mm/yyyy): _____

Date of randomization visit (dd/mm/yyyy): _____

Vessel being considered for treatment

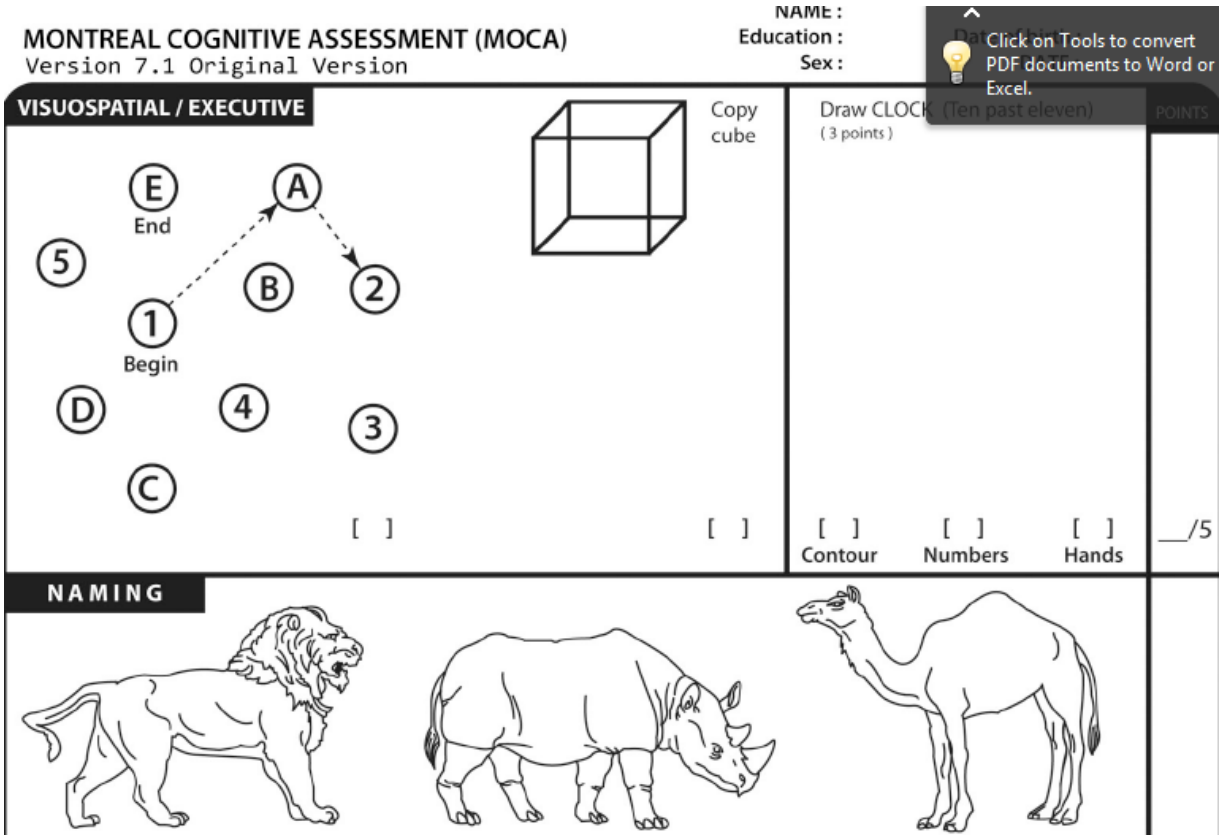
Paper versions of all the documents will be sent to your centre as PDF files so that they can be printed out as necessary. There will also be links to these forms on our website www.ecst-2.com

Paper forms that are required to be completed and entered online:

- Screening Form
- Baseline Data Collection Form
- Surgical/Stenting Technical Form
- 48 hour Follow up Data Collection Form (only required in patients receiving carotid revascularisation)
- One month/6 weeks Follow up Form
- Follow up Form (for 6 month and yearly follow up appointments)
- Telephone Follow up Form
- Withdrawal form
- Stroke/TIA event form
- Death Event Form
- Myocardial Infarction Event form
- Crossover Form

Forms that are required to be completed and sent directly to Central Trial Office

- Personal Data and NOK form Version 1.1
- Montreal Cognitive assessment



You are required to write on the Follow up forms how the patient scored in the MoCA and then send a copy of the actual assessment to the Central Trial Office.

The questions from the EQ5D form are incorporated into the online forms; therefore you are not required to send copies of the paper EQ5D to the office.

Rankin Focused Assessment

In ECST-2 we are using the Rankin Focussed Assessment (RFA) to assess the level of disability. The purpose of the focused assessment is to assign patients a mRs grade in a systematic way.

Modified Rankin Scale	
6	**Dead**
5	**Severe disability**: bedridden, incontinent and requiring constant nursing care and attention.
4	**Moderately severe disability**: unable to walk without assistance, and unable to attend to own bodily needs without assistance.
3	**Moderate disability**: requiring some help, but able to walk without assistance.
2	**Slight disability**: unable to carry out all routine activities but able to look after own affairs without assistance.
1	**No significant disability:** despite symptoms: able to carry out all usual duties and activities.
0	**No disability**

If the patient is 'asymptomatic' we can use the 'Prestroke Rankin Focussed Assessment' (see below).

Prestroke Modified Rankin Scale	
5	**Severe disability**: bedridden, incontinent and requiring constant nursing care and attention.
4	**Moderately severe disability**: unable to walk without assistance, and unable to attend to own bodily needs without assistance.
3	**Moderate disability**: requiring some help, but able to walk without assistance.
2	**Slight disability**: unable to carry out all routine activities but able to look after own affairs without assistance.
1	**No significant disability:** despite symptoms: able to carry out all usual duties and activities.
0	**No disability**

The links to the Structured Interview forms and Training Package are on our website (www.ecst2.com).

List of Abbreviations:

CDU – Carotid Doppler Ultrasound
CAR – Carotid Artery Risk Score
CAS – Carotid Artery Stenting
CEA – Carotid Endarterectomy
CT – Computed Tomography
DWI,ADC – Diffusion weighted imaging, apparent diffusion coefficients (MRI sequence)
ECG – electrocardiogram
FLAIR – Fluid attenuated inversion recovery (MRI sequence)
GRE – Gradient Echo (MRI sequence)
MRI – Magnetic Resonance Imaging
mRs – Modified Rankin Score
MoCA – Montreal Cognitive Assessment
OMT – Optimised Medical Treatment

Contact Details

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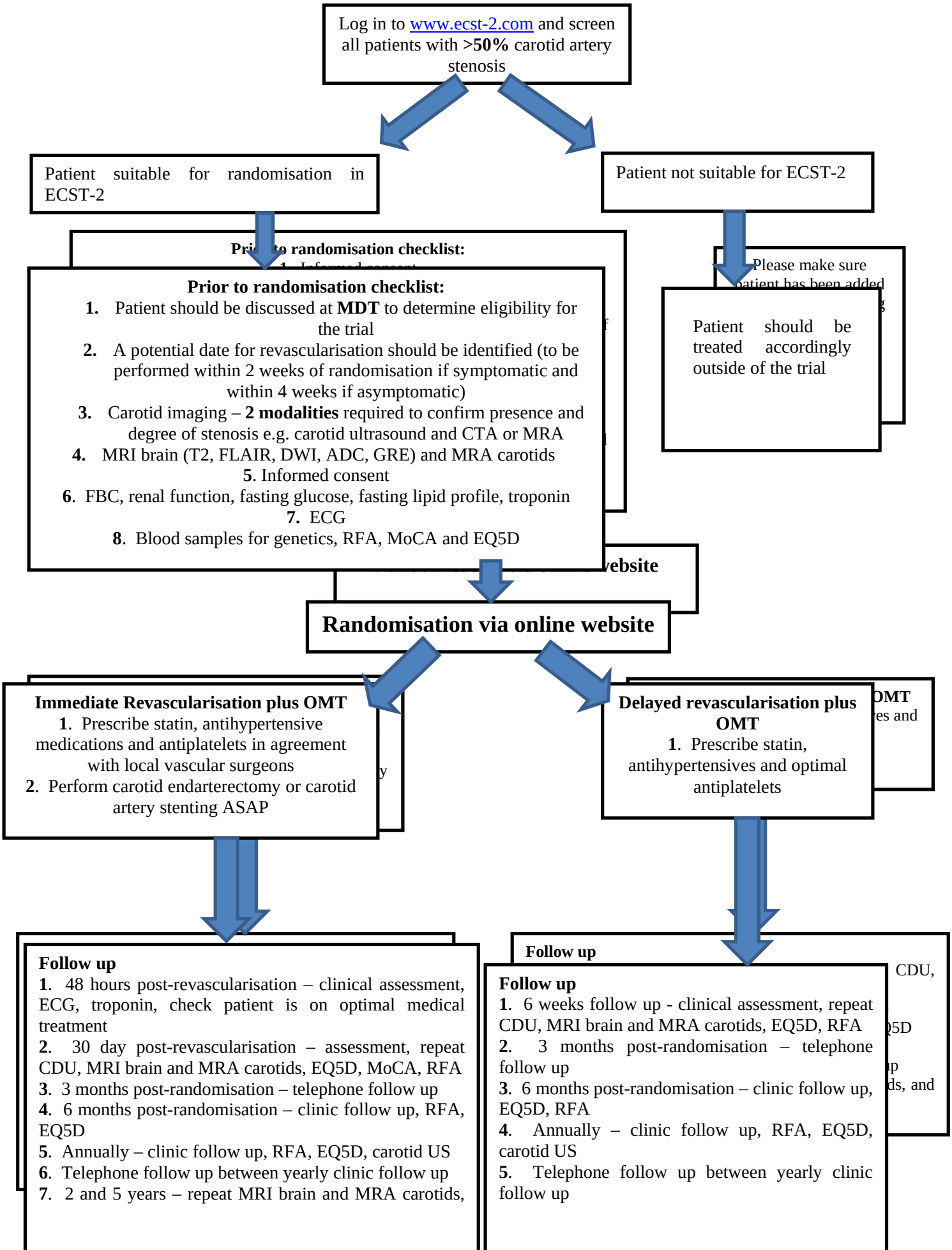
Log in to www.ecst-2.com and screen all patients with >50% carotid artery stenosis
Patient suitable for randomisation in ECST-2
Patient not suitable for ECST-2
Prior to randomisation checklist:
1. Patient should be discussed at MDT to determine eligibility for the trial
2. A potential date for revascularisation should be identified (to be performed within 2 weeks of randomisation if symptomatic and within 4 weeks if asymptomatic)
3. Carotid imaging – 2 modalities required to confirm presence and degree of stenosis e.g. carotid ultrasound and CTA or MRA
4. MRI brain (T2, FLAIR, DWI, ADC, GRE) and MRA carotids
5. Informed consent
6. FBC, renal function, fasting glucose, fasting lipid profile, troponin
7. ECG
8. Blood samples for genetics, RFA, MoCA and EQ5D
Please make sure patient has been added
Patient should be treated accordingly outside of the trial
Randomisation via online website
Immediate Revascularisation plus OMT
1. Prescribe statin, antihypertensive medications and antiplatelets in agreement with local vascular surgeons
2. Perform carotid endarterectomy or carotid artery stenting ASAP
Delayed revascularisation plus OMT
1. Prescribe statin, antihypertensives and optimal antiplatelets
Follow up
1. 48 hours post-revascularisation – clinical assessment, ECG, troponin, check patient is on optimal medical treatment
2. 30 day post-revascularisation – assessment, repeat CDU, MRI brain and MRA carotids, EQ5D, MoCA, RFA
3. 3 months post-randomisation – telephone follow up
4. 6 months post-randomisation – clinic follow up, RFA, EQ5D
5. Annually – clinic follow up, RFA, EQ5D, carotid US
6. Telephone follow up between yearly clinic follow up
7. 2 and 5 years – repeat MRI brain and MRA carotids,
Follow up
1. 6 weeks follow up - clinical assessment, repeat CDU, MRI brain and MRA carotids, EQ5D, RFA
2. 3 months post-randomisation – telephone follow up
3. 6 months post-randomisation – clinic follow up, EQ5D, RFA
4. Annually – clinic follow up, RFA, EQ5D, carotid US
5. Telephone follow up between yearly clinic follow up