NHS Research Ethics Committee
APPLICATION FORM

This form should be completed by the Chief Investigator, after reading the guidance notes.
See Glossary for clarification of different terms in the application form.

Short title and version number (maximum 70 characters - this will be inserted as header on all forms):
ACST-2 version 3.2

Name of NHS research ethics committee to which application for ethical review is being made:
Hertfordshire 1

Project Reference number from above REC: 05/Q0201/66
Submission Date: 16/09/2005

PART A

A1. Title of Research

Full title: ACST -2: Asymptomatic Carotid Surgery Trial-2: surgery vs stenting

Key words: Randomised controlled trial; clinical trial; vascular surgery; carotid artery disease; carotid angioplasty and stenting; carotid endarterectomy

A2. Chief Investigator

Title: Miss First Name/Initials: Alison Last Name: Halliday
Post: Consultant Vascular Surgeon & Reader
Qualifications: Consultant Vascular Surgeon
Organisation: St George's University of London
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A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with application.

A3. Proposed Study Dates and Duration

Start date: 01/09/2005

End date: 01/09/2015

Duration Years 10 Months

A4. Primary purpose of the research: *(Tick as appropriate)*

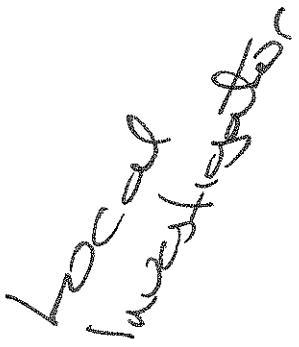
- ☐ Commercial product development and/or licensing
- ☒ Publicly funded trial or scientific investigation
- ☐ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

A5. Tick the box if your research:

- ☐ involves testing a medicinal product
- ☒ involves investigating a medical device
- ☐ involves additional radiation above that required for clinical care
- ☐ involves using stored samples of human biological material (e.g. blood, tissue)
- ☐ involves taking new samples of human biological material
- ☐ involves only patient records or data, with no direct patient contact
- ☐ involves prisoners or others in custodial care
- ☐ involves adults with incapacity
- ☐ has the primary aim of being educational (eg student research, a project necessary for a postgraduate degree or diploma, other than an MD or PhD)

A6. Do you consider that this research falls within the category where there is no local investigator?

YES ☐ NO ☑



Advice can be found in the Guidance Notes on this topic. Some studies do not require further consideration of site-specific issues by NHS Research Ethics Committees, but will still require approval to proceed from the host organisation(s).

A7. What is the principal research question/objective? *(Must be in language comprehensible to a lay person.)*

Patients with substantial narrowing (stenosis) of the carotid artery, a main blood supply to the brain, have increased stroke risk. Strokes happen when the brain's blood supply is disrupted. A recent trial has shown that surgical removal of the narrowing (carotid endarterectomy) in patients who have had no stroke like symptoms in the previous 6 months (asymptomatic) can substantially reduce the risk of stroke compared to those that had medical treatment alone. Carotid artery stenting (placing a wire mesh which holds the artery open) is a new method of treating carotid narrowing which is rapidly gaining popularity. However, there is very little evidence that it is safer or even equivalent to treating with carotid surgery. A multicentre randomised trial comparing carotid stenting with carotid endarterectomy (CEA) in patients with tight asymptomatic carotid artery narrowing is therefore needed. The principal research questions are:

1) What are the differences in clinical myocardial infarction (heart attack) rates and in stroke and death within 30 days of carotid stenting compared with carotid endarterectomy?

2) What is the difference in the long-term (5-year) survival, free of disabling or fatal stroke for carotid stenting versus carotid endarterectomy?

A8. What are the secondary research questions/objectives? *(If applicable. Must be in language comprehensible to a lay person.)*

3) What is the rate of re-narrowing of the carotid artery after stenting compared with surgery, causing symptoms of stroke?

4) What is the cost-effectiveness of carotid stenting compared with surgery?

A9. What is the scientific justification for the research? What is the background? Why is this an area of importance? *(Must be in language comprehensible to a lay person.)*

In the UK stroke is responsible for 12% of all deaths. Carotid artery stenosis is a well recognised cause of stroke. At least one million people in Europe alone have severe narrowing of one or both of their carotid arteries (60-99% stenosis). Appropriate medical treatment including blood thinning and cholesterol-lowering therapy is standard for patients at high risk of both heart attack and stroke. However, patients with carotid stenosis have a higher stroke risk which cannot be reduced by these medical treatments alone.

Since the publication in 1991 of two large trials comparing surgery with non-surgical care (ECST and NASCET), CEA has become an effective, well-recognised treatment for stroke prevention in symptomatic patients (stroke-like symptoms <6 months previously). In 2004, the Asymptomatic Carotid Surgery Trial (ACST) looked at "asymptomatic" patients with similar carotid stenoses but no stroke or stroke-like warning symptoms within the previous 6 months. Patients (aged less than 75 years and with a stenosis of 70% or more) had their overall 5-year stroke risk halved from about 12% to about 6%. Therefore, there is now large scale randomised controlled trial evidence supporting surgery in appropriate asymptomatic patients and these findings are expected to change future practice. Carotid artery stenting is a new method of treating carotid stenosis. A wire and catheter is introduced through a groin artery, and by X-ray monitoring is passed into the carotid artery. The narrow portion is ballooned, then a cylindrical wiremesh is placed across the stenosis and pushed open to hold the narrow artery sides apart. Advantages of carotid artery stenting may include shortened hospital stay, fewer wound related complications (discomfort, nerve damage, bruising and infection) and fewer heart attacks within the first 30 days following surgery. However, stenting may pose increased risks as stent expansion does not remove the compressed narrowing during stent placement, and so a diseased portion of artery may crumble and cause a stroke by blocking the blood supply to the brain. There may also be an increased risk of re-narrowing with carotid stenting as compared to CEA. The concept and comfort of stenting may be more acceptable to the patient than surgery, but the 'track record' of CEA is well established and, with experienced surgeons, risks and overall benefit are clear and reliable.

There is very little recent evidence that stenting is safer, or even equivalent to CEA in early efficacy and long-term (5-year) stroke prevention. Nevertheless, the procedure, often performed under local anaesthetic, is rapidly gaining popularity amongst doctors, especially cardiologists, and is expected to continue increasing in popularity.

Current randomised trials comparing carotid stenting with endarterectomy' are being undertaken in mainly symptomatic patients (ICSS, SPACE, EVA-3S, CREST).The only recent trial with a proportion of asymptomatic patients, SAPPHIRE, randomised 334 patients at so called surgical 'high risk' between CEA and stenting. This trial had very small numbers and a skewed patient population. They concluded that carotid stenting was 'not inferior' to CEA in these patients but the statistical analysis and relevance of the results of SAPPHIRE have been questioned and much larger trials are now needed. No trial has yet been undertaken specifically for asymptomatic patients. A new multicentre trial, ACST-2, is therefore being set up to answer this clinically important question so that patients and doctors are better informed before chosing surgery or stenting for asymptomatic carotid stenosis.

A10. Give a brief synopsis/summary of methods and overview of the planned research. This should include a brief description of how prospective research participants and concerned communities (not necessarily geographical) from which they are drawn have been consulted over the design and details of the research. *(Where appropriate a flow chart or diagram should be submitted separately. It should be clear exactly what will happen to the research participant, how many times and in what order.)*

An overview of the planned research is given below:
The "uncertainty" principle (whereby individual physicians are uncertain about which treatment is best for a patient, rather than collective professional uncertainty) will be used to enable the patient population to be as heterogeneous as possible - as all doctors have differences, however small, in choosing whether patients are suitable for a randomised study, each doctors' 'area of uncertainty' would be used to enable ethical decisions to be made by doctor and patient before entering the trial. If the doctor or the patient felt that one treatment would be more appropriate, the patient would not be entered.
1.Identification and assessment of potentially eligible participants: Patients will generally be identified from surgical or medical clinics. As the carotid stenosis is asymptomatic, patients will normally have presented with other vascular problems. ALL patients with uni- or bilateral carotid stenosis for whom the collaborating doctor is uncertain whether to treat with carotid surgery or carotid stenting will be considered. Patients in the trial will not undergo any extra examinations other than those routinely performed. Prior to randomisation, the percentage of stenosis in both carotid arteries will be estimated using non-invasive duplex ultrasound examination. Assessment and treatment of risk factors (such as diabetes, hypertension, hypercholesterolaemia) is extremely important for all patients. Neurological examination and, if indicated, a brain scan will be undertaken. If coronary artery bypass/grafting (or angioplasty) is needed, this should be done before entering the trial.
2. Randomisation and treatment: If the carotid artery under consideration is asymptomatic for 6 months or more, the doctor and the patient feel that the patient is fit and willing for operation OR stenting and follow-up, and the patient has given written informed consent to take part in the trial, the patient will be entered into the trial and randomised either to carotid surgery or carotid stenting. Allocated treatment will be carried out as soon as routinely possible. A procedural follow-up form will be completed 30 days after the operation or stenting. This will require neurological re-examination of the patient including non-invasive duplex ultrasound of both carotids. A major event follow-up form will also be completed if there have been any strokes, deaths or procedural heart attacks in the 30 days since the treatment.
3. Further follow-up: will be by yearly telephone call for at least 5 years ideally by a neurologist or physician with an interest in stroke. Information collected will include whether they have had a stroke or stroke-like symptoms, any other carotid surgery or stenting, and details of current medication. If the patient has had any neurological symtoms (not stroke) they should be seen and assessed promptly by neurologist / stroke physician (or other appropriately trained clinical staff). If the patient has a stroke, they should again be seen promptly by neurologist / stroke physician and a major event form should be completed and sent to the ACST-2 office. If the patient has any further carotid stents or carotid surgery a procedural follow-up form should be completed 30 days after the intervention. Any patient deaths should be reported to the ACST-2 office via a major event form.
4. Patients GP details will be collected at the time of the randomisation and GPs will be informed that the patient is taking part in the trial. To minimise loss to follow-up, GPs may also be contacted for follow-up information if the collaborator loses contact with the patient (e.g. patient moves). Patients will be 'flagged' with the Office of National Statistics. The central co-ordinating office will thus be informed directly of any patient deaths and of patients that have moved, therefore the trial co-ordinating centre will be able to trace their new GP without the patient having to directly contact their trial collaborator.

All patients will be given a patient information sheet and be asked to provide written informed consent to all the above.
This randomised controlled trial will not be blinded as both the patient and the observers will be aware of the patient's treatment. The study methodology has been developed with a statistician. Inconvenience to patients and doctors taking part in this trial has been kept to a minimum. After treatment and 1 month procedural follow-up, patients will only be contacted once a year by telephone unless they have a stroke or stroke-like symptoms and therefore need to attend hospital to see a neurologist/stroke physician (as is normal practice). Both carotid stenting and carotid surgery carry risks of stroke and death. In the case of carotid surgery, these risks are well documented. However, to minimise risks for those undergoing carotid stenting and carotid surgery, collaborators carrying out these procedures will have to meet certain criteria proving their competancy before they can join the study. An independent Data Monitoring Committee will be set up to confidentially review interim analyses.
Concerned communities such as vascular surgeons, radiologists and cardiologists have been consulted during the design of this research. Research results will be fed back to particpants via the trial collaborators.
The trial is expected to start recruitment in late 2005. The recruitment period will last 5-8 years with final analysis of results in 2010-2013.

A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?

YES ☐ NO ☑

A12. Will the research participants receive any clinical intervention(s) or procedure(s) including taking samples of human biological material over and above that which would normally be considered a part of routine clinical care?

YES ☐ NO ☑

A13. Will the research participant be subject to any non-clinical research-related intervention(s) or procedure(s)?

YES ☑ NO ☐

Additional intervention	Average number per patient		Average time taken (mins/hrs /days)	Details of additional intervention or procedure, who will undertake it, and what training they have received.
	Routine Care	Research		
Telephone interview		1 per year	10 mins	Telephone interview with patient ideally by the collaborating neurologist or physician with an interest in stroke, all of whom have experience interacting with patients. Information collected will include whether they have had a stroke or stroke-like symptoms, had any other carotid surgery or stenting, and details of current medication. Patients may also be asked to up-date their GP contact details.

Please give details for any other(s):

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?

YES ☐ NO ☑

The Information Sheet should make it clear under what circumstances action may be taken

A15. What is the expected total duration of participation in the study for each participant?

Up to 10 years (to give overall 5-year results).

A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, medical devices, ionising radiation, or from other interventions (including non-clinical):

Myocardial infarction, stroke and death within 30 days of stent or operation. To minimise these risks, collaborators carrying out these procedures will have to meet certain criteria proving their competancy before they can join the study. The surgeons will already have experience in undertaking CEA. The surgeon collaborators will submit a track record of their results to the ACST-2 office. This will consist of the results of their last 50 CEAs, which should ensure they are performing CEAwithin accepted trial guidelines (<8% stroke and death risk for symptomatic patients and ~3% risk for asymptomatic patients). They should be performing at least 10 CEAs per year. Interventionalists carrying out carotid stenting will also be asked to submit a 'track record' prior to participation in ACST-2 which will be reviewed by a technical management sub-committee. They must recently have carried out at least 50 stenting procedures involving aortic arch access; most should be in the carotid territory with an acceptable outcome. Centres that do not yet have enough experience to become a participating centre in the trial will be asked to undergo further training. Participating centres will be asked to provide yearly logs of surgical and stenting activity with clinical (30 day) outcomes.

A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?

Carotid artery stenting and operation may involve some pain, discomfort, distress and inconvenience for the patient, as would any similar procedure. However, in order to take part in the study, the collaborator and patient must have already made the decision to carry out a procedure on the patient for their asymptomatic carotid narrowing (rather than continuing with medical treatment alone), despite their risks. The collaborator should therefore only be 'uncertain' whether to carry out an operation or stenting to clear the narrowing.

After the procedure, further pain, discomfort, distress and inconvenience to the patient has been kept to a minimum. Apart from a neurological follow-up 30 days after the procedure including a non-invasive duplex ultrasound, the patient will only be contacted once a year by telephone for follow-up information.

A18. What is the potential for benefit for research participants?

There are no direct benefits to be gained by the research participant through taking part in the research, except perhaps monitoring over a longer than normal period (yearly telephone interview for at least 5 years).

A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress or inconvenience for the *researchers* themselves? *(if any)*

None apart from monitoring of patients over a longer than normal period (yearly telephone interview for at least 5 years) - but this is minimal inconvenience.

A20. How will potential research participants in the study be *(i)* identified, *(ii)* approached and *(iii)* recruited?
Give details for cases and controls separately if appropriate:

i) Patients will be identified from surgical or medical clinics. As the carotid stenosis is asymptomatic, patients will normally have presented with other vascular problems such as peripheral vascular disease and diabetes.

ii) During the surgical/medical clinics, the collaborating surgeon, neurologist, stroke physician or cardiologist will identify any patients matching the study entry criteria. The collaborator (or designated research nurse or other designated member of the clinical team) will then approach the patient and discuss the study with them and provide them with a patient information sheet (see attached) which contains information on all aspects of the study including background information and rationale for the study, all procedures that may be involved and details of the anticipated follow-up about the study. It will be stressed that the patient's participation in the trial is entirely voluntary and they can withdraw at anytime. The patient will be encouraged to discuss participation in the study with family as well as medical staff. If the patient agrees to take part they will be given a consent form to read and, after having unlimited time to decide whether to take part in the study, they will be asked to sign the consent form agreeing to take part. The patient will be given a copy of the signed agreement and the patient information sheet to take home.

iii) If the patient decides to enter the study they will then be randomised (by telephone randomisation) to either carotid artery operation or stenting. Allocated treatment will take place as soon as routinely possible. Randomisation will take place at the computerised central randomisation service at the Clinical Trials Service Unit (CTSU) in Oxford.

A21. Will research participants be recruited via advertisement?

YES ☐ NO ☑

A22. What are the principal inclusion criteria? *(Please justify.)*

Patients eligible if in the view of the responsible collaborator:
1) Patients have unilateral or bilateral carotid artery stenosis appropriate for surgery or stenting. The severity of stenosis is not defined specifically - some will have stenoses >90% and some may have stenosis of ~50% with soft plaque; patients with contralateral occlusion may be randomised. The patient may be entered into the trial if the collaborator is satisfied that the lesion is clinically and technically appropriate for carotid surgery or stenting.
2) Patients' carotid stenosis has not caused symptoms for at least 6 months, they have no past history of disabling or severe contralateral stroke, and have no contra-indications to carotid endarterectomy or carotid stenting.
3) The patient is fit for, and willing to have carotid surgery or stenting and accessible for follow-up, with no known illness preventing long-term follow-up.
4)There is substantial uncertainty about whether the patient is better treated by surgery or stenting.

A23. What are the principal exclusion criteria? *(Please justify.)*

Reasons for not entering patients into the trial are specified by the responsible collaborator, not by the protocol, but include:
1) a small likelihood of worthwhile benefit such as low risk of cerebral infarction from a smooth calcified carotid plaque not causing significant stenosis or some major life-threatening disease other than stroke.
2) a high risk of adverse effects of trial treatment such as recent acute myocardial infarction or intracerebral neoplasia or aneurysm.
3) those found unsuitable for stenting or surgery after angiography (e.g. because the lesion is surgically inaccessible or because the aortic arch anatomy is difficult for stenting access).
4) re-narrowing of the artery following previous CEA or stent.
5) patients with a likely cardiac source of emboli.
6) patients unable or unwilling to give informed consent.

A24. Will the participants be from any of the following groups? *(Tick as appropriate.)*

- ☐ Children under 16
- ☐ Adults with learning disabilities
- ☐ Adults who are unconscious or very severely ill
- ☐ Adults who have a terminal illness
- ☐ Adults in emergency situations
- ☐ Adults with mental illness (particularly if detained under mental health legislation)
- ☐ Adults suffering from dementia
- ☐ Prisoners
- ☐ Young Offenders
- ☐ Adults in Scotland who are unable to consent for themselves
- ☐ Healthy volunteers
- ☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
- ☐ Other vulnerable groups

Justify their inclusion:

It is not intended to enter any patients into the study from the above groups. However, as many of the patients taking part in the study will be elderly (expected age range 40-75 years) some may develop conditions associated with old age e.g. serious illness, dementia, and some may eventually be in care homes. These will be dealt with on a case by case basis and in consultation with the patient's treating physicians. Some participants may become demented during follow-up and therefore we may need to seek follow-up information from relatives, carers or GP.

A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?

What steps will you take to find out? YES ☐ NO ☐ Not Known ☑

A26. Will informed consent be obtained from the research participants?

YES ☑ NO ☐

Give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.

If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe the arrangements to be made for obtaining consent from a legal representative.

The collaborator (or designated research nurse or other designated member of the clinical care team) will be the person that discusses the study with the patient, provides them with a patient information sheet about the study (see attached) and, in due course obtains written informed consent. It will be stressed that the patient's participation in the trial is entirely voluntary and they can withdraw at anytime. The patient can keep the patient information sheet and will be encouraged to discuss their participation with the local collaborator, their GP and family as appropriate. They will have unlimited time to decide whether to enter the study. A copy of the signed consent form should be kept in the patient's notes and a copy sent to the ACST-2 office.
A website containing other background material will also be available to those with internet access.
There will be no participants from potentially vulnerable groups.

Copies of the written information and all other explanatory material should accompany this application

A27. Will a signed record of consent be obtained?

YES ☑ NO ☐

Attach a copy of the consent form to be used, with a version number and date.

A28. How long will the participant have to decide whether to take part in the research?

As long as they need (usually within one month but longer if necessary).

A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English? *(e.g. translation, use of interpreters etc.)*

These patients would not be included.

A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The co-ordinating centre will keep abreast of current relevant research via automated literature searches and attending scientific meetings. Any new information that becomes available which might affect the patient's decision to continue to take part in the research will be disseminated to the collaborators so that they can inform their patients in the study.

A31. Does this study have, or require, approval of PIAG (Patient Information Advisory Group) or other bodies with a similar remit? *(see Guidance Notes)*

YES ☐ NO ☑

A32. Will the research participant's General Practitioner be informed that they are taking part in the study?

YES ☑ NO ☐

Enclose a copy of the information sheet/letter for the GP with a version number and date.

Will permission be sought from the research participants to inform their GP before this is done?

YES ☑ NO ☐

It should be made clear in the patient information sheet if the research participant's GP will be informed.

A33. Will individual research participants receive any *payments* for taking part in this research?

YES ☐ NO ☑

A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?

YES ☐ NO ☑

A35. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for *negligent* harm?

As this is University sponsored non-commercial research the provisions within HSG(96) 48, reference 2. apply to this project. The clinical researcher involved in this project (Miss Alison Halliday) has a contract with St. George's University of London as a clinical researcher.

Please forward copies of the relevant documents

A36. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for *non-negligent* harm?

As this is University sponsored non-commercial research, no provisions exist for non-negligent harm to participants. Participants suffering injury as a result of having taken part in this research will need to pursue a claim for negligence through standard litigation procedures.

Please forward copies of the relevant documents

A37. How is it intended the results of the study will be reported and disseminated? *(Tick as appropriate)*

- ☒ Peer reviewed scientific journals
- ☐ Internal report
- ☒ Conference presentation
- ☐ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ Written feedback to research participants
- ☐ Presentation to participants or relevant community groups
- ☐ Other/none e.g. Cochrane Review, University Library

A38. How will the results of the research be made available to research participants and communities from which they are drawn?

Collaborators will inform participants of the main results of the study at its close and the results will also be disseminated by peer reviewed publication and will be available on the trial website.

A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)? *(Tick as appropriate)*

- ☒ Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- ☐ Electronic transfer by magnetic or optical media, email, or computer networks
- ☐ Sharing of data with other organisations
- ☐ Export of data outside the European Union
- ☒ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☒ Storage of personal data on any of the following:
  - ☒ Manual files including X-rays
  - ☐ NHS computers
  - ☐ Home or other personal computers
  - ☒ University computers
  - ☐ Private company computers
  - ☐ Laptop computer

Further details:

Occasionally, it will be necessary to provide the central co-ordinating centre (based at a medical school) with copies of information from the patient's medical record so that major events can be properly audited e.g. copy of CT scan if patient has had a stroke.
The co-ordinating centre will also keep a record of personal addresses, postcodes, telephone numbers and NHS numbers of the participants. This information is necessary to 'flag' patients with the Office of National Statistics. The patients will not be contacted by the central co-ordinating centre at any time.
These personal data and any manual patient files will be kept in locked cupboards. Similarly, the patient database on the Medical School computer system will be secure and meet Data Protection Act regulations.

A40. What measures will be put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures will be used, and at what stage:

Randomisation of patients will take place either by telephone or by fax to the randomisation unit in the Clinical Trial Services Unit, Oxford. Transfer of randomisation data from Oxford to the central co-ordinating centre in St George's hospital will take place by secure transfer, either by encrypted email or by directly downloading to the trial database by secure FTP transfer. The data will be held on a secure password protected database which will be stored on a secure password protected server on the medical school computing system. Patient data will be entered using initials, date of birth and trial number so that they cannot be identified. Due to the nature of the work it would be extremeley difficult to completely anonymise the database. However, trial staff will only have access to data appropriate to their role. All ACST staff agree to maintain confidentiality at all times as part of their employment contract with University of London. All manual patient files will be kept in locked cupboards and the office will meet all Data Protection Act regulations as directed by the Data Protection Officer at SGUL, John Duffy.

A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?

The analysis of the data will take place at the Clinical Trial Services Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford, OX3 7LF. The analysis will be supervised by Professor Rory Collins (statistician).

to completely anonymise the database. However, trial staff will only have access to data appropriate to their role. All ACST staff agree to maintain confidentiality at all times as part of their employment contract with University of London. All manual patient files will be kept in locked cupboards and the office will meet all Data Protection Act regulations as directed by the Data Protection Officer John Duffy, Director of Administration at SGUL.

A42. Who will have control of, and act as the custodian for, the data generated by the study?

The principal investigator, Miss Alison Halliday, and co-investigator, Professor Richard Peto.

A43. Who will have access to the data generated by the study?

The research staff at the central co-ordinating centre and involved staff at the Clinical Trial Services Unit, Oxford. Collaborators in the study will have access to data from their own centres, if requested.

Any other requests for data will be discussed by the Trial Steering Committee on a case by case basis but in no circumstances will patient identifiable information be provided to those outside the immediate research team.

A44. For how long will data from the study be stored? 10 Years [ ] Months

Give details of where they will be stored, who will have access, and of the custodial arrangements for the data:

Manual patient files will be kept in the co-ordinating centre (Medical School) in locked storage. The database will be kept on the Univerisy computer server (see above). A copy of the database will also be downloaded and kept in a safe in the co-ordinating centre. Only the immediate research team will have access to the data. Any other requests for data will be discussed by the Trial Steering Committee on a case by case basis but in no circumstances will patient identifiable information be provided to those outside the immediate research team

A45. How has the scientific quality of the research been assessed? *(Tick as appropriate)*

- ☐ Independent external review
- ☐ Review within a company
- ☒ Review within a multi-centre research group
- ☒ Internal review (e.g. involving colleagues, academic supervisor)
- ☐ None external to the investigator
- ☐ Other, e.g. methodological guidelines

If you are not in possession of any referees' or other scientific critique reports relevant to your proposed study, justify and describe the review process and outcome. If review has been undertaken but not seen by the researcher, give the details of the body which has undertaken the review:

The protocol has been designed with the aid of the Clinical Trial Sevice Unit, University of Oxford. Its scientific quality has been thoroughly assessed by the Unit who have many years experience of planning and carrying out such studies. The protocol will undergo independent review as the full funding application has now been submitted.

A copy of any referees' comments or other scientific critique reports relevant to the proposed research must be enclosed with the application form.

A46. Has similar research on this topic been done before? YES ☑ NO ☐

Why should it be repeated?

A trial with a small number of asymptomatic patients, SAPPHIRE, randomised patients at so called surgical 'high risk' between CEA and stenting. This trial had very small numbers and a skewed patient population. They concluded that carotid stenting was 'not inferior' to CEA in these patients but the statistical analysis and relevance of the results of SAPPHIRE have been questioned. The question of the potential benefit of carotid stenting compared to surgery remains unanswered. A large and more streamlined trial is required both to reliably assess the superiority of either CEA or carotid stenting and to ensure these results are generalisable to the population at large with asymptomatic carotid artery disease.

A47. Have all existing sources of evidence, especially systematic reviews, been fully considered? YES ☑ NO ☐

Please give details of search strategy used:

Online databases such as Medline, Embase, Web of Science were searched for relevant articles. The Cochrane database of systematic reviews and the National Institute for Clinical Excellence website were also searched. Relevant meeting abstract books were inspected for the latest research. Discussion also took place with researchers in the field to obtain information on unpublished studies.

A48. What is the primary outcome measure for the study?

1) What are the differences in clinical myocardial infarction rates and in stroke and death within 30 days of carotid stenting compared with carotid endarterectomy?
2) What is the difference in the long-term (5-year) survival free of disabling or fatal stroke for carotid stenting versus carotid endarterectomy?

A49. What are the secondary outcome measures? *(If any)*

3) What is the rate of re-narrowing of the carotid artery after stenting compared with surgery causing symptoms of stroke?
4) What is the cost-effectiveness of carotid stenting compared with surgery?

A50. How many participants will be recruited? How many of these participants will be in a control group?

The recruitment target is 4000+ patients. 50% of patients will be in the 'control' group (the CEA group).

A51. Has the size of the study been informed by a formal statistical power calculation?

YES ☑ NO ☐

Indicate the basis upon which this was done and give sufficient information to allow the replication of the calculation:

The calculation below has informed the size of the study and this shows that 4000+ patients will be required to provide this.

An increase of about 60% in the stroke rate with stenting versus surgery (e.g. 5% vs 3%, respectively), and a decrease of about 60% in the myocardial infarction rate with stenting versus surgery (e.g. 0.8% vs 2%, respectively), could both be detected with 90% statistical power at 2P<0.05.

A52. Has a statistician given an opinion about the statistical aspects of the research?

YES ☑ NO ☐

Give the name and contact details:

Professor Richard Peto, Clinical Trials Service Unit, Richard Doll Building, Old Road Campus, Oxford OX3 7LF
Tel: 01865 743743 Fax: 01865 743985

Give a brief summary of advice offered and attach a copy of the comments if available:

The sample size was based on discussions with the statisticians and other relevant investigators.

Enclose a copy of comments. If the comments are not available then please enclose a summary of the opinion.

A53. Describe the statistical methods and/or other relevant methodological approaches (e.g. for qualitative research) to be used in the analysis of the results. Give details of the methods of randomisation process to be used if applicable:

Statistical analysis of results: the results will be analysed using Kaplan-Meier life-table analyses. Logrank analyses will compare event rate between all those allocated carotid stenting and all those allocated CEA (irrespective of treatment given i.e. intention to treat analysis) at specified time periods.

Randomisation : minimised randomisation and stratified for gender, age, centre, degree of stenosis and experience of collaborator (assessed by track record). Randomisation will be by telephone and will take place at the computerised central randomisation service at the Clinical Trials Service Unit (CTSU) in Oxford. Data will then be downloaded to the ACST-2 database by secure encrypted email or FTP transfer.

A54. Where will the research take place? *(Tick as appropriate)*

- ☑ UK
- ☑ Other States in the European Union
- ☑ Other States in the European Economic Area
- ☑ Other

Give details:

This will be a worldwide multi-centre study. However, the majority of centres are expected to be in Europe.

All participating centres will have to provide written evidence of appropriate ethical approval before they can take part in the study.

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or in the European Economic Area?

YES ☐ NO ☑

A56. In how many and what type of host organisations (NHS or other) in the UK is it intended that the proposed study will take place?

Indicate the type of organisation by ticking the box and give approximate numbers if known:

		Number of organisations
☒	Acute teaching NHS Trusts	
☒	Acute NHS Trusts	
☐	NHS Community and/or Primary Care Trusts	
☐	NHS Trusts providing mental healthcare	
☐	NHS Care Trusts	
☐	Social Care Organisations	
☐	Prisons	
☒	Independent hospitals	
☐	Educational establishments	
☐	Independent research units	
☐	Other (give details)	

A57. What arrangements are in place for monitoring and auditing the conduct of the research?

The trial will be managed by a trial steering committee which will include the principal investigators, independent health professionals in relevant fields and patient representatives. The Data Monitoring Committee will look at the data periodically through interim analyses. Regular progress reports will be submitted to the funders.
If patients are recruited from St George's Hospital the Trust will conduct monitoring and auditing exercises. Otherwise central monitoring for completion, plausibility outcomes and other aspects of data integrity will be conducted by the Trial Co-ordinating Centre at SGUL in liaison with the Trial Steering Committee and the Data Monitoring Committee.

Will a data monitoring committee be convened? YES ☑ NO ☐

What are the criteria for electively stopping the trial or other research prematurely?

The Data Monitoring Committee will look at major event data at interim analyses and advise the Trial Steering Committee whether there is an unacceptably high morbidity associated with surgery or stenting (either overall or in particular centres), or if there is clear evidence that for all or some particular types of patient, there is proof beyond all reasonable doubt that one or the other procedure is preferable.

Details of membership of the Data Monitoring Committee, their standard operating procedures and summaries of reports of interim analyses to the Data Monitoring Committee must be forwarded to the NHS research ethics committee approving the study.

A58. Has funding for the research been secured? YES ☐ NO ☑

What arrangements are being made to cover any costs of the research? If no external funding is being sought, please say so:

Funding has been secured for 1 year for the Senior ProgrammerData Manager.

External funding is being sought to cover the following:

Staff:
Trial Co-ordinator (full-time) - Total for 5 years is £214,961 (inc. NI, Superannuation and London Allowance)
Assistant Administrator (full-time) - Total for 5 years £164,202 (inc. NI, Superannuation and London Allowance)
Senior ProgrammerData Manager (full-time) - Total for 5 years is £214,961 (inc. NI, Superannuation and London Allowance)

Other costs: Total cost for 5 years is £416,910 for items listed below:
Administration (printing, stationary, telephone and fax charges, photocopying)
Equipment (fax machine, telephones, computers, printer)
Travel (to visit collaborating centres)

A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?

YES ☐ NO ☐ Not yet known ☑

Has the employer of the Chief Investigator agreed to act as sponsor of the research?

YES ☑ NO ☐ Not yet known ☐

Give details of the organisation who will act as the sponsor of the research:

Organisation:	St Georges University of London
Address:	Cranmer Terrace London
Postcode:	SW17 0RE
UK Contact:	Mary Anne Tourette
Telephone:	020 8725 1012 Fax: 020 8725 3426
Email:	mtourett@sgul.ac.uk

A copy of documentation indicating that the organisation has accepted the role of sponsor should be enclosed if the sponsor is not the main funder, the Chief Investigator's employer, or an NHS body hosting the research.

A60. Has any responsibility for the research been delegated to a subcontractor?

YES ☐ NO ☑

A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?

YES ☐ NO ☑

A62. Will individual *researchers* receive any other benefits or incentives for undertaking this research?

YES ☐ NO ☑

A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?

YES ☐ NO ☑

A64. Does the Chief Investigator or any other key investigator/collaborator have any direct personal involvement (e.g. financial, share-holding, personal relationship etc.) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

YES ☐ NO ☑

A65. Other relevant reference numbers if known *(give details and version numbers as appropriate):*

Applicant's/organisation's own reference number, e.g. R&D (if available):	
Sponsor's/protocol number:	
Funder's reference number:	
International Standard Randomized Controlled Trial Number (ISRCTN):	
European Clinical Trials Database (EUDRACT) Number:	
Project website:	www.acst.org.uk (initially)

A66. Other key investigators/collaborators *(all grant co-applicants should be listed)*

i	Title:	Prof	First Name/Initials: Richard	Last Name:	Peto
	Post:	Co Director of CTSU and Professor of Medical Statistics and Epidemiology at Univ. of Osford			
	Qualifications:	BA MSc (Statistics)			
	Organisation:	Clincal Trial Services Unit (CTSU)			
	Address:	CTSU, Richard Doll Building, Old Road Drive Roosevelt Road Oxford		Telephone: Fax:	01865 743743 01865 743985
	Postcode:	OX3 7LF	Email:	secretary@ctsu.ox.ac.uk	
ii	Title:	Dr	First Name/Initials: Dafydd	Last Name:	Thomas
	Post:	Consultant Neurologist			
	Qualifications:	MD			
	Organisation:	St Mary's Hospital, London			
	Address:	Praed Street London		Telephone: Fax:	020 7725 1389 020 7725 6200
	Postcode:	W2 1NY	Email:	dafydd.thomas@ic.ac.uk	
iii	Title:	Prof	First Name/Initials: Jean-Pierre	Last Name:	Becquemin
	Post:	Professor of Vascular Surgery			
	Qualifications:	MD			
	Organisation:	Hospital Henri Mondor			
	Address:	51 Avenue du Mal de Lattre de Tassigny 94010 Creteil Cedex France		Telephone: Fax:	33 1 49812433 33 149812435
	Postcode:		Email:	jpbecquemin@hotmail.com	
iv	Title:		First Name/Initials:	Last Name:	
	Post:				
	Qualifications:				
	Organisation:				
	Address:			Telephone: Fax:	
	Postcode:		Email:		
v	Title:		First Name/Initials:	Last Name:	
	Post:				
	Qualifications:				
	Organisation:				
	Address:			Telephone: Fax:	
	Postcode:		Email:		

If there are more than 5 collaborators, please enter at end of section or attach a further sheet.

A67. If the research involves a specific intervention, (e.g. a drug, medical device, dietary manipulation, lifestyle change, etc.), what arrangements are being made for continued provision of this for the participant (if appropriate) once the research has finished?

N/A

Summary of Ethical Issues

A68. What do you consider to be the main ethical issues or problems which may arise with the proposed study, and what steps will be taken to address these?

There are no ethical problems arising from the proposed study.

A69. Do you need to add further information about certain questions in Part A?

YES ☐ NO ☑

PART B: Section 2 - Investigation of Medical Devices

1. Give details of the medical device(s) to be used in the study

i. Device description: Carotid Wallstent

Manufacturer: Boston Scientific

Use: To hold open a narrowed carotid artery.

Length of use: Does the device have a CE mark?* YES ☑ NO ☐

ii. Device description: Smart

Manufacturer: CORDIS

Use: To hold open a narrowed carotid artery.

Length of use: Does the device have a CE mark?* YES ☑ NO ☐

iii. Device description: Acculink

Manufacturer: Guidant

Use: To hold open a narrowed carotid artery.

Length of use: Does the device have a CE mark?* YES ☑ NO ☐

**For all products with a CE mark please attach instructions for use.*

2. Does the study involve the use of a *new* medical device or *new* implantable material or the use of an existing product outside the terms of its CE marked intended purpose?

YES ☐ NO ☑

3. For electrical devices give summarised details of acceptance and safety testing

N/A

4. Is a medical device company or other commercial company arranging this trial?

YES ☐ NO ☑

a) Is this trial a clinical investigation requiring notification to the MHRA? YES ☐ NO ☑

b) Does the company have a Notice of No Objection from the MHRA? YES ☐ NO ☐

c) Has MHRA approval been applied for but not yet received? YES ☐ NO ☐

Note: An application can be made prior to receipt of a valid Notice of No Objection from MHRA. The Notice will be issued subject to the sponsor subsequently receiving a favourable opinion. There is no requirement for a valid Notice of No Objection to be provided to the relevant ethics committee before the research can be given a favourable opinion.

5. Have any of the medical devices been transferred from one organisation (legal entity) to another for the purpose of this trial?

YES ☐ NO ☑

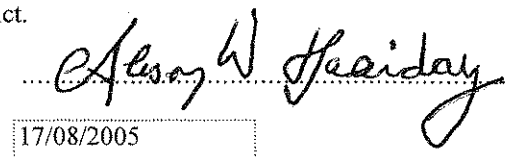
6. In cases of equipment or medical devices, what arrangements have been made with the manufacturer to provide indemnity?

None, as all devices are approved and not experimental normal clinical negligence regulations apply.

Enclose a copy of the relevant correspondence, with a version number and date.

PART B: Section 7 - Declaration

- The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
- I undertake to abide by the ethical principles underlying the Declaration of Helsinki, and Good Practice Guidelines on the proper conduct of research.
- If the research is approved I undertake to adhere to the study protocol without unagreed deviation and to comply with any conditions set out in the letter sent by the NHS Research Ethics Committee notifying me of this.
- I undertake to inform the NHS Research Ethics Committee of any changes in the protocol, and to submit annual reports setting out the progress of the research.
- I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.
- I understand that research records/data may be subject to inspection for audit purposes if required in future.
- I understand that personal data about me as a researcher in this application will be held by the Research Ethics Committee and its operational managers, and that this will be managed according to the principles established in the Data Protection Act.

Signature of the Chief Investigator: 

Date: 17/08/2005

Print Name: Alison Halliday

1. Do you need to add further information about certain questions in Part B?

YES ☑ NO ☐

ENSURE THAT YOU COMPLETE AND SIGN THE FORM, AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS.

B1-1. Further information for Part B

(Please specify the question number to which the information applies)

Q1 - Give details of the medical device(s) to be used in the study:

i. Device description: Mednova Neuroshield
Manufacturer: Abbott
Use: To prevent emboli getting to brain
Does the device have a CE mark: YES

Device description: Angioguard
Manufacturer: CORDIS
Use: To prevent emboli getting to brain
Does the device have a CE mark: YES

Device description: EPI
Manufacturer: Boston Scientific
Use: To prevent emboli getting to brain
Does the device have a CE mark: YES

Device description: PercuSurge
Manufacturer: Medtronic
Use: To prevent emboli getting to brain
Does the device have a CE mark: YES

Device description: Parodi Anti-Emboli System
Manufacturer: ArteriA Medical Science Inc.
Use: To prevent emboli getting to brain
Does the device have a CE mark: YES