

The Asymptomatic Carotid Surgery Trial (ACST) Rationale and Design

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Key Words: Carotid artery stenosis; Carotid endarterectomy; Plaque characterisation; Randomised clinical trial; Stroke.

Introduction

The current incidence of stroke in Europe and the U.S.A. is about 200 per 100,000 population per annum.^{1,2} Eighty percent of strokes are ischaemic and 20% are due to haemorrhage. Approximately half the patients with ischaemic stroke³ have carotid artery stenosis and about one-third (~10% all stroke victims) have had no warning symptoms such as transient ischaemic attacks.⁴

The European Carotid Surgery Trial (ECST)⁵ and North American Symptomatic Carotid Endarterectomy Trial (NASCET)⁶ have effectively shown that carotid endarterectomy (CEA) can prevent strokes and death in *symptomatic* patients. The benefit of operation is, at present, confined to those with at least 70% stenosis; for 30-69%, the trials have not yet reported a result. There is as yet no convincing evidence in *asymptomatic* patients that stroke (or death) can be prevented by CEA. The aim of this trial is to determine whether CEA and appropriate best medical treatment (BMT) can improve stroke-free survival time when compared with BMT alone.

Background

Asymptomatic carotid stenosis (ACS) can be accurately and non-invasively detected by ultrasound.^{7,8} It is often found in patients with contralateral symptomatic stenosis, or vascular disease elsewhere, but routine ultrasound screening is also justified in certain

population groups. Stenosis of more than 50% is present in ~25% hypertensive patients,⁹ and in ~12% of those with peripheral vascular disease. Other groups worth screening include those over 60 years who are known to have ischaemic heart disease, aneurysms or hyperlipidaemia, and are currently smokers.¹⁰⁻¹²

ACS may be an important causative factor in unheralded stroke. Two factors, accurately detectable by ultrasound, are particularly important: severity of stenosis and composition of the stenotic plaque. Approximately three-quarters of strokes which do occur in natural history studies of ACS are ipsilateral to the side with severe stenosis, implicating the carotid stenosis as the cause of stroke.¹³ Bilateral stenosis may carry even greater risk, especially if the patient has an incomplete circle of Willis. There is evidence of higher risk in patients with contralateral occlusion, reduced collateral circulation (measured by transcranial doppler) and progressively occlusive carotid disease.¹⁴

The type of plaque causing stenosis appears to have important prognostic significance. Ultrasonically echolucent material is, when examined histologically, soft and friable, and echogenic plaque is fibrotic and collagenous.¹⁵ Several studies have demonstrated that patients with predominantly 'soft' plaques are more likely to have suffered previous TIAs or strokes.¹⁶⁻¹⁹ Prospectively, by following patients using serial ultrasound, Langsfield and Bock found that both plaque type and degree of stenosis were positively associated with subsequent development of symptoms.^{20,21}

Although stroke risk is thought to be greatest with stenoses >80%, Satiani showed that patients with >50% stenosis had a 7% risk of stroke after 2 years²² and Moore found that after 5 years one-third of

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hypertensive patients with similar stenoses had had a stroke.²³ Johnson reported that "even patients with <75% narrowing are at increased risk if the plaque was heterogeneous or soft", and after 3 years, 20% of patients in this study had either had a TIA or stroke.²⁴ Clearly an effective preventative therapy was needed.

Medical Treatment of ACS

Treatment of modifiable medical risk factors is appropriate in all patients. Meta-analysis of hypertension trials showed that reduction of systolic blood pressure by 5–6 mm Hg was associated with 35–40% fewer strokes and 20–25% fewer myocardial infarctions.²⁵ Regular aspirin usage has been found to reduce deaths from myocardial infarction and non-fatal strokes in symptomatic patients.²⁶ Lipid-lowering therapy may, by reducing total and LDL cholesterol and fibrinogen, effect plaque regression.²⁷ It has certainly been shown to reduce the incidence of symptomatic coronary heart disease. Control of diabetes is important as, although strokes may still occur, prevention of hyperglycaemia may attenuate stroke severity.²⁸ Smoking directly affects the incidence of carotid stenosis and although there is no evidence yet to suggest that stopping smoking will slow, stop or reverse ACS, it should be strongly discouraged.²⁹ Heavy alcohol consumption has been associated with hypertension and haemorrhagic stroke and should be reduced.³⁰ Myocardial infarction is commoner than stroke in patients with ACS and discovery of carotid stenosis is a golden opportunity to uncover and treat heart disease.³¹ Patients with ACS may be non-invasively investigated by ECG and exercise testing, or by modified studies such as ECG chest wall mapping or dipyridamole-thallium exercise scanning.³² In some cases, coronary angiography and subsequent angioplasty or bypass surgery may be necessary. The asymptomatic carotid artery does not usually have to be operated upon when coronary artery bypass is undertaken.³³

Surgery for ACS

Because carotid endarterectomy can be performed with low perioperative morbidity and mortality, surgeons may be tempted to operate. In a recent collective review of over 2300 endarterectomies for ACS, Colburn found that the perioperative stroke rate and 30-day mortality was 1.5% and 0.8%.³⁴

Comparisons of outcome with and without surgery may suggest that surgery is beneficial; Moneta in 1987 reported that 19% patients with >80% stenosis had strokes or died within 2 years, in contrast to 5.8% of the surgically treated group.³⁵ Bias occurs within non-randomised trials however, and even 'natural history' studies do not include patients who have been preselected for surgery, potentially altering results.

Clinical Trials of ACS

The ideal means of investigating the importance of ACS should be a clinical trial. The North American and European *symptomatic* carotid surgery trials (ECST and NASCET) have successfully demonstrated the value of endarterectomy for symptomatic carotid stenosis.^{5,6} But, to date, four trials of surgery for ACS have been inconclusive.

The Mayo Clinic trial compared aspirin with surgery and was terminated after only 71 patients had been entered because an excess of patients in the surgical group had myocardial infarctions.³⁶

CASANOVA, a German trial, took 10 years, reporting in 1991.³⁷ Four-hundred-and-ten patients in 10 centres were entered. All were given aspirin and were completely asymptomatic. Patients with >90% stenosis were excluded, and several different treatment options such as unilateral or bilateral endarterectomy, and unilateral endarterectomy or medical treatment were permitted. Operative intervention occurred frequently during medical patients' follow-up (e.g. if bilateral stenoses exceeded 50%). The trial end points were stroke and death. The trial was stopped when only 122 patients who had unilateral surgery were available for comparison with 111 who had medical treatment. At this point only 9.8% of the unilateral surgical group and 12.6% of the medical group had reached an endpoint ($p=0.321$). The trial organisers concluded that "at least 2000 randomised patients are needed to detect 25–33% reduction of stroke risk ... (and this information) ... will not be available from one single study but will require meta-analysis of all available trials".

The Veterans' Administration trial (#167) ran from 1983–91.³⁸ Only men were eligible and 444 out of a target of 500 were recruited. Patients with previous ipsilateral cerebral infarction (clinical or CT) were excluded and the endpoints were TIA, stroke and death. After TIA, crossover to surgery was permitted. For stroke prevention, results were again inconclusive, but 12.8% of the surgical group had stroke or TIAs compared with 24.8% of the medical group. They

concluded that "to detect a reduction of 50% in strokes in the surgical group would require more than 3000 patients — beyond the scope of any contemporary clinical trial" in ACS.

Currently, the largest clinical trial is the Asymptomatic Carotid Artery Study (ACAS) in the U.S.A. and this has recruited about 1500 patients. Certain minimum entry criteria are obtained and the minimum preoperative stenosis is 60%, with angiography compulsory only in the operated group.³⁹ Endpoints are, like the VA trial, TIA, stroke or death.⁴⁰ At the present time there are insufficient data to report results. However, as the VA trial showed, TIA is not the endpoint necessary to answer the fundamental question posed by all these trials — 'does carotid endarterectomy prevent stroke?' Only about one-third of patients who reach an end-point have stroke as their first event. Many patients will be needed to determine the place of surgery in preventing stroke in ACS. If endarterectomy prevents stroke we need to know which types of plaques and severity of stenoses *detected non-invasively* are most important when making the decision to invasively investigate or operate. Some clinicians believe that because they *can* do the operation with very low morbidity and mortality, this justifies the procedure. The ACST will help determine the place of surgery in caring for these patients.

The Asymptomatic Carotid Surgery Trial (ACST)

Aim of the trial

This is a multicentre randomised trial of CEA in patients with asymptomatic carotid artery stenosis.

The aim is to determine whether CEA and BMT improve stroke-free survival time when compared with BMT alone. The trial will also help identify high risk groups in whom the benefits of surgery and of BMT would be increased.

Eligibility

Patients whose carotid stenosis has not caused symptoms for at least 6 months, who have no past history of ipsilateral disabling or severe contralateral stroke, and have no clear indications for, or contra-indications to, carotid endarterectomy, are eligible for ACST. Patients already in ECST cannot be entered into this Trial as a patient can only be randomised once, even though they have two carotid arteries. The participating

Neurologist should ensure that they are asymptomatic. If they have residual neurological signs *but have nevertheless no symptoms to specific questioning*, then they are asymptomatic. The presence of residual signs should be recorded by the neurologist and the patient considered eligible for the trial. It is well known that the commonest cause of death in patients with carotid stenosis is ischaemic heart disease and screening for this, even in patients without symptoms is strongly encouraged.

Patients are therefore eligible if in the view of the responsible physician or surgeon:-

- 1) They have unilateral or bilateral carotid artery stenosis appropriate for surgery. The severity of stenosis is not defined specifically — some patients will have unilateral occlusion, some will have stenoses >90% and some may have stenosis of ~50% with soft plaque. **The patient may be entered into ACST if the surgeon is satisfied that the lesion is clinically and technically appropriate to operate on, if randomised to that option.**
- 2) The patient is fit for, and willing to have surgery if recommended and accessible for follow-up, with no known illness preventing longterm follow-up.
- 3) There is *substantial uncertainty* about whether the patient is better treated by surgery and appropriate medical treatment or by medical therapy alone.

Reasons for **not entering** patients into the Trial are specified by the responsible surgeon or physician, not by the protocol but include:-

- 1) a small likelihood of worthwhile benefit such as:-
 - (i) low risk of cerebral infarction from a smooth calcified carotid plaque not causing significant stenosis;
 - (ii) some major life-threatening disease other than stroke;
- 2) a high risk of adverse effects of trial treatment such as:-
 - (i) recent acute myocardial infarction;
 - (ii) intracerebral neoplasia or aneurysm.
- 3) Restenosis of the artery following previous CEA

The degree of consent is left to individual doctors to decide for individual patients in the light of any advice they may receive from their local Ethical Committee. In some centres written consent may be required; verbal consent or informal discussion may be considered adequate in other centres but any consent required should be sought *before* randomisation. At all times the local requirements for operative

surgery consent should be met and if necessary, a full description of the operation and perioperative care provided. This should also be taken to include appropriate consent for invasive radiological procedures if they are undertaken in trial patients. The collaborating surgeons and physicians will be responsible for patient care in the normal way and the trial should not alter their normal practice.

Choice of Treatments

Best medical treatment (for ALL patients)

Patients' 'best medical treatment' is extremely important. Risk factors for stroke and death (the trial's end-points) specifically targetted are smoking, hypertension, diabetes, obesity, hyperlipidaemias, polycythaemia and ischaemic heart disease. These should all be rigorously managed.

As randomisation will be within centres slight differences in medical management between centres should not influence overall results but all centres will be expected to ensure that patients receive optimal care. Although treatment is only recorded at trial follow-up, it should be strictly adhered to and the controlling physician should, by appropriately frequent visits, ensure patient compliance.

Smoking should be strongly discouraged and if possible stopped completely.

Hypertension should be controlled within 'safe' limits (a systolic blood pressure consistently > 160 mmHg and a diastolic pressure consistently > 100 mmHg may be generally considered to confer a higher than normal risk of stroke).

Diabetes should be recognised, treated and controlled.

Ischaemic Heart Disease, whether symptomatic or uncovered by investigation should be appropriately treated. Treatment of coronary artery disease by angioplasty or by-pass surgery is *not* a contra-indication for future entry into ACST (however in this trial CEA cannot be performed simultaneously with coronary bypass surgery). **Entry into ACST should be as soon as the patient is considered fit for further surgery after bypass or angioplasty has been successfully performed.**

Hyperlipidaemia should be treated. Cholesterol level should ideally be < 5.0 mmol/l.

Anti-coagulant drugs may be given as part of treatment for other conditions, e.g. mitral valve replacement or as part of therapy for disease related to carotid stenosis, e.g. femoro-distal by-pass grafting using PTFE.

Antiplatelet therapy may be considered as 'best medical treatment' unless the patient is already on longterm anticoagulants, e.g. warfarin or there is a specific contra-indication to aspirin or ticlopidine treatment such as allergy or gastrointestinal haemorrhage.

Surgical treatment (50% patients)

Carotid endarterectomy should be carried out as soon as routinely possible if the patient is randomised to surgical treatment. The surgeon may wish to undertake preoperative angiography before or after randomisation. This is not mandatory as many surgeons now perform CEA without angiography.

CEA may not be scheduled before, or at the same time as planned elective coronary artery by-pass surgery. The carotid endarterectomy technique is that with which the individual surgeon is familiar. Specific procedures, such as shunting, are undertaken at the surgeon's discretion.

It is expected that the surgeons collaborating in this trial will already have experience in undertaking CEA in patients who are symptomatic and have clear clinical indications for surgery. The surgeon collaborators should have a track record of their own results which should compare favourably with standards elsewhere in Europe and the U.S.A. Before becoming a collaborator in ACST, each surgeon submits a record of their last 50 endarterectomies, specifying the number done for asymptomatic disease, and the number of disabling strokes or deaths occurring within 30 days of surgery. They should keep on-going records of their results and will be asked on a yearly basis to submit the numbers of CEAs undertaken with indications for surgery. Specific results will not be requested for operations outside the Trial. However, if an individual surgeon's results in this Trial show an unacceptably high morbidity or mortality (as found by the Audit Committee) they may be asked not to enter any further patients. Complete follow-up on those already entered will be necessary and the collaborator would be asked to continue within the Trial on a 'follow-up only' basis.

Following surgery, and before discharge patients should be assessed by the neurologist to ensure there is no neurological deficit (if one is uncovered, the patient should be investigated for stroke and the major event form completed and returned). Routine postoperative and follow-up treatment usually includes antiplatelet therapy.

Surgical complications — stroke or death

No surgery form is required by the ACST office. However, if the patient has a stroke or dies, a major event form must be filled out and returned as soon as possible. All details which may be relevant (e.g. operative procedure, postoperative course and complications) should be recorded within the patient's notes and will then be of help in filling out the major event form. As major events will eventually provide the Trial end points, these details are of vital importance. A telephone call or fax should be sent to the ACST office to indicate that surgical complications have occurred, *as soon as the events take place*; details can be provided then on the form.

Telephone randomisation: made easy with the randomisation notepad (Fig. 1)

No entry form is needed for ACST and no unusual tests are required. Entry is by means of a direct dial telephone call (or fax) to the randomisation service in Oxford to answer a few questions about the patient. Calls should be made between 0900–1700 U.K. time. The telephone call is *made easier and quicker* by use of the randomisation notepad to prepare answers for the questions:-

- a) Name and country of surgeon or agreed collaborator in charge.
- b) Patient name, date of birth, sex.
- c) Relative - name and phone number (or address) (in U.K. give GP's name and postcode)
- d) Current therapy and blood pressure
- e) Carotid artery history, evidence of infarct on brain scan, presence of echolucent plaque and estimate (%) of carotid stenosis.
- f) Intention (if surgery drawn) to operate on left or right artery.

At the end of the telephone call after the pre-randomisation details have been provided, the randomisation service allocates the patient's treatment; either best medical treatment and surgery, or best medical treatment alone. All patients are then irrevocably in the trial whether treatment is carried out or not since the trial analysis will be on 'intention to treat'.

Surgery should therefore be carried out as soon as possible on a planned elective basis, and any surgical complications reported as soon as they occur.

ASYMPTOMATIC CAROTID SURGERY TRIAL
RANDOMISATION — Answer ALL questions

Then phone: 0900-1700 UK time, weekdays, or if unable to phone, you can fax:
England: (44) 865-240972 England (44) 865-728003. Reply within 1 working day.
Incomplete lists will be sent back for further details.
N.B. Return fax number must be enclosed.

N.B. Patients in ECST must not be entered.

1. Surgeon / Country: _____

2. Patient's family name: _____

3. Patient's given name: _____

4. Patient's date of birth (day, month, year):

5. (UK or Holland) GP's surname and postcode: _____

6. (Not UK & Holland) Relative (not husband/wife) name, phone no. (+ area code) + address:
Name: _____ Telephone no.: _____
Address: _____

(N.B. * means tick 1 answer ONLY)

*7. Male <input type="checkbox"/>	Female <input type="checkbox"/>	YES	NO
*8. Diabetic		<input type="checkbox"/>	<input type="checkbox"/>
*9. Definite coronary artery disease		<input type="checkbox"/>	<input type="checkbox"/>
*10. Needs coronary bypass or angioplasty		<input type="checkbox"/>	<input type="checkbox"/>
*11. Currently taking: antihypertensive therapy		<input type="checkbox"/>	<input type="checkbox"/>
*12. " " antiplatelet therapy		<input type="checkbox"/>	<input type="checkbox"/>
*13. " " anticoagulant therapy		<input type="checkbox"/>	<input type="checkbox"/>
*14. " " lipid lowering therapy		<input type="checkbox"/>	<input type="checkbox"/>

15. Total cholesterol (mmVL): _____ OR mg/100 ml:

16. Present blood pressure (mm Hg): Systolic: Diastolic:

17. Duplex doppler % stenosis Left: Right:

*18. Is more than 25% of the plaque soft (echolucent)?
Left Right Both None Don't know

*19. Infarct on CT scan Left Right Both None Not done

*20. Infarct on MRI scan Left Right Both None Not done

*21. Which side are you considering surgery for? Left Right

*22. Any prior symptoms this side >6 months ago?
None Amaurosis Cortical Stroke Other
TIA

*23. Any prior contralateral symptoms? None Amaurosis Cortical Stroke Other
TIA

*24. Previous CEA Left Right No

Information to be obtained from phone call: _____ Date:

Treatment allocated:
Best medical treatment and surgery
or Best medical treatment alone

Fig. 1. The simple randomisation notepad.

Follow-up and the development of symptoms or major events

In contrast to ECST, the surgeon is usually the physician who screens for, detects and initially assesses the majority of patients with asymptomatic carotid stenosis. This may not be the case in all European countries or in all practices.

Follow-up in all patients is often the role of the surgeon, as many neurologists do not wish to follow up asymptomatic patients. During trial follow-up all patients should be seen at 4 months after randomisation, 12 months, and yearly thereafter. An up-to-date Duplex Doppler examination of both carotid arteries should be carried out at each follow-up visit. The follow-up is simple, requiring answers for the questions:-

- a) Name of surgeon or agreed collaborator, date
- b) If randomised to surgery; date and side, any clinical myocardial infarct

- c) Any other carotid surgery since last follow-up; date, side
- d) Any carotid symptoms either side; stroke, death, date
- e) Current Duplex stenosis, any definite increase in plaque echolucency
- f) Current drug therapy and blood pressure

If patients develop neurological symptoms (not stroke) they must be seen and assessed promptly by the neurologist. If the patient has a stroke, assessment by the collaborating neurologist (including CT scan) should be carried out promptly and a major event form completed and returned to the ACST office. Appropriate clinical action should be taken which may include patients on medical treatment alone going on to have CEA. This *does not* exclude them from the trial and follow-up should continue on the same basis for all patients. All patients remain within the trial until the trial is completed.

If the patient dies, the major event form should be completed and returned. **There is only *one* double sided form to return**, covering follow-up *and* major events.

Analysis

Main and subsidiary analyses

The main comparisons will be of:-

1. Stroke and death rates in medical treatment plus surgery group versus medical treatment alone in the first 4 months after randomisation and at yearly intervals to 5 years.
2. Duplex results in the medical treatment plus surgery group versus those having medical treatment alone at the same intervals as in 1.

Subsidiary analyses will include:-

The effect of risk factors e.g., groups with no CT or MR infarction compared with those with e.g., definite ipsilateral areas of infarction on outcome.

Other exploratory analyses will be performed to examine the data available thoroughly.

Interim analyses — the data monitoring committee

During the study interim analyses of major events will be supplied to the Data Monitoring Committee. They will advise the Steering Committee whether there is an unacceptably high morbidity associated with surgery. During follow-up further interim analyses will be carried out.

The Data Monitoring Committee will advise the Steering Committee if there is 1) proof beyond reasonable doubt that for all or some types of patient one particular treatment is contraindicated in terms of net difference in mortality and 2) evidence that might reasonably be expected to influence materially patient management by clinicians who are already aware of the results of other main trials. 'Reasonable doubt' cannot be specified precisely but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying the study.

Should this happen and one treatment is clearly indicated or contra-indicated in terms of net difference in mortality or stroke the trial would thereby influence patient management and would either be stopped or modified to seek extra data. The Trial Committee and collaborators will otherwise remain ignorant of interim results. The overall survival and major stroke free survival curves for both treatment groups will be analysed. These may cross because of greater hazards initially in the surgical group during the perioperative period. Similar life table analyses will be used to compare the survival in unoperated groups with soft (echolucent) Gray Weale Type 1 & 2, and echodense (Gray Weale Type 3 & 4) carotid plaques of differing stenoses. As no minimum stenosis has been specified (such as > 60% in ACAS), the range of stenoses found and proportion of plaque types cannot be predicted until recruitment is well under way (although few patients will have < 50% stenosis).

Validation of the Doppler technique will not be formally tested in each collaborating centre. It has been the practice of a number of centres to perform CEA without angiography for some years. Centres who screen with Doppler *and* perform angiograms may be requested by the Data Monitoring Committee, to provide angiography films on a randomly selected sample of patients, to ensure that the relationship between Doppler stenosis and angiography has a positive predictive value of around 90%.

All patients undergoing CEA at each centre should be logged locally and a reason for not putting them in the trial should be recorded, e.g. patient in ECST, or symptomatic with a > 70% stenosis. A yearly request for local CEA logs will be sent to each centre.

Conclusion

A simple trial has been launched to answer the question 'Does carotid endarterectomy prevent disabling stroke or death in patients with asymptomatic

carotid artery stenosis?' The normal practice of collaborating surgeons and physicians will be studied, and appropriate best medical treatment will be given to all trial patients. In addition to medical treatment, one half of patients will undergo carotid endarterectomy. Entering patients in ACST is simple and the trial is designed to minimise extra work for busy collaborators.

Organisation

Trial Steering Committee (St Mary's Hospital, London)

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Local Organising Committee (St Mary's Hospital)

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Data Monitoring Committee

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Prof. Charles Warlow, Edinburgh

Audit Committee

Dr Rodney Foale, St Mary's Hospital
Prof. Michael Harrison, The Middlesex Hospital
Prof. Vaughan Ruckley, Edinburgh

Statistics and Randomisation (Clinical Trials' Service
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Dr Rory Collins
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National Co-ordinators (to date)

Bulgaria — Dr V. Petrov, Sofia

Cyprus — Dr N. S. Angelides, Nicosia
England — Mr B. Campbell, Exeter
Germany — Prof. W. Sandmann, Dusseldorf
Ireland — Prof. G. Shanik, Dublin
Israel — Dr B. Yoffe, Ashkelon
Italy — Dr P. Cao, Perugia
The Netherlands — Prof. B. Eikelboom, Utrecht
Norway — Prof. H. Myhre, Trondheim
Poland — Prof. M. Szostek, Warsaw
Portugal — Prof. J. Fernandes e Fernandes, Lisbon
Spain — Prof. M. Cairols, Barcelona
Sweden — Prof. D. Bergqvist, Malmö
Yugoslavia — Dr D. Radak, Belgrade

Acknowledgements

We are grateful to The Stroke Association of Great Britain and Ireland for funding this study and for support received from the NorthWest Thames Regional Research Fund.

The Clinical Trials' Service Unit, Oxford and ECST have provided considerable and generous help with study design and randomisation.

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Accepted 1 March 1994