

Trial Protocol

ISAT

INTERNATIONAL
SUBARACNOID
ANEURYSM TRIAL



**THE INTERNATIONAL
SUBARACHNOID
ANEURYSM TRIAL**

**FUNDED BY
THE MEDICAL RESEARCH
COUNCIL
OF GREAT BRITAIN.**

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INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL (ISAT)

A RANDOMISED TRIAL OF SURGERY COMPARED WITH ENDOVASCULAR THERAPY IN THE TREATMENT OF RUPTURED INTRACRANIAL ANEURYSMS APPROVED BY THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN.

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Steering Committee:

Chairman

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Members

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Trialists

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ISAT steering committee terms of reference

1. To monitor and supervise the progress of the **Randomised trial of surgery compared with endovascular therapy in the treatment of intracranial aneurysms (ISAT)** towards its interim and overall objectives.
2. To review at regular intervals relevant information from other sources (e.g. other related trials).
3. To consider recommendations of the data monitoring committee and local ethics committees.
4. In the light of 1,2 and 3 to inform the Medical Research Council UK (MRC) and the Health Services and Public Health Research Board (HSPHRB) on the progress of this trial.
5. To advise HSPHRB on publicity and the presentation of all aspects of this trial.

The Data Monitoring Committee

Prof Charles Warlow, Consultant Neurologist,
Department of Clinical Neurosciences University of Edinburgh,
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Dr Richard Greenhall, Consultant Neurologist, Radcliffe Infirmary.
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Data monitoring committee terms of reference

- 1 To determine how frequently interim analysis of trial data should be undertaken.
- 2 To consider the unblinded interim data from the **Randomised trial of surgery compared with endovascular therapy in the treatment of intracranial aneurysms (ISAT)** and relevant information from other sources.
- 3 In the light of II and ensuring that ethical considerations are of prime importance, to report (following each DMC meeting) to the trial steering committee and to recommend whether the trial should continue, the protocol be modified or the trial be stopped.
- 4 To consider any requests for unblinding and release of interim trial data and to recommend to the trial steering committee on the importance of this.

Notes

- a. Members of the DMC will remain independent of the trial staff and steering committee.
- b. The trial statistician will be invited to attend each DMC meeting to present the most current unblinded data from the trial.

Executive group terms of reference

- 1 The trial executive group are responsible for the daily operations of the study at the co-ordinating centre in Oxford.
- 2 They will meet approximately once per month to consider issues raised during the monthly progress of the study.
- 3 The executive group liaises with the steering committee, the data management centre and statistical centre.
- 4 The executive group consists of:
 - The principal neurosurgical investigator
 - The principal radiological investigator
 - An experienced trialist
 - The trial co-ordinators
 - Statistician
 - Other members such as health economist and neuropsychologist who will attend meetings as appropriate.

ISAT Executive Group

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ISAT Statistician

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ISAT Data Management

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ISAT Neuropsychological Analysis

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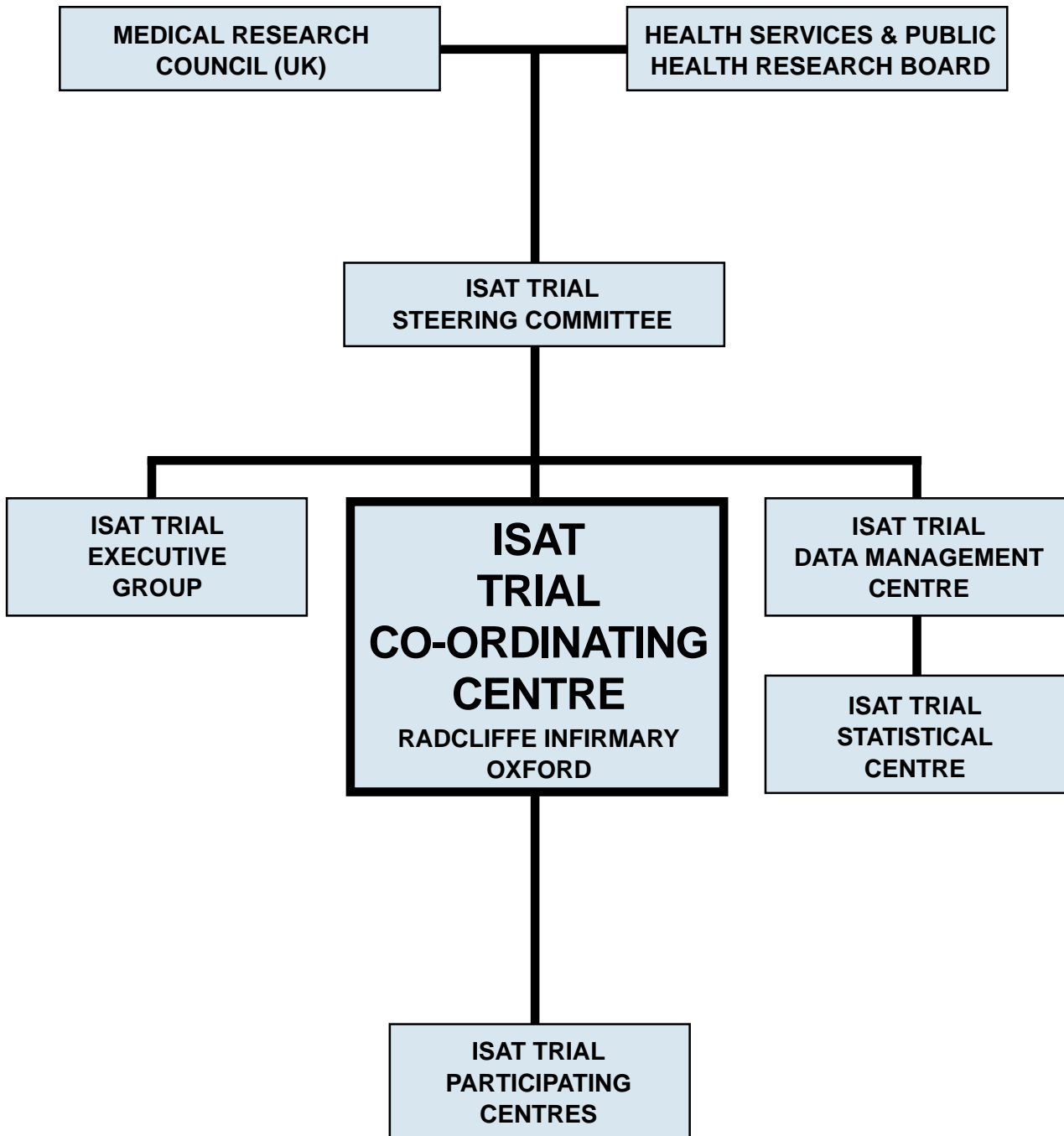
ISAT Health Economics Analysis

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ISAT TRIAL ORGANISATION CHART



STUDY OVERVIEW

Trial background

Aneurysmal subarachnoid haemorrhage (SAH) is a significant cause of death and continuing disability in relatively young patients with an annual incidence of between 6 and 12 per 100,000¹² population in most western countries. The natural history of the disease is such that over 30% of patients will die within 24 hours of the bleed and a further 25-30% will succumb in the next four weeks without some form of surgical intervention¹.

The publication of the International Co-operative Study on the Timing of Aneurysm Surgery provided the most extensive data to date on the results of modern management in a large number of patients treated in experienced neurosurgical centres². Over 3,000 patients were entered in a prospective observational study from 1980 to 1983. The results showed that the overall mortality rates in the surgical patients were between 20% and 28% depending on the timing of surgery and the grade of the patient. Patients in grade 3/4 (stuporose or comatose) had mortality rates between 39% and 79%. Overall good outcomes occurred in approximately 60% of patients, leaving approximately 20% of patients with residual morbidity. Of the patients planned for surgery between 11 and 14 days, 14% rebled pre-operatively. Many of these rebleeds were either fatal or resulted in a significantly poorer outcome. More recent surgical series of selected patients from experienced centres have suggested lower rates of serious morbidity and mortality following surgery³. e.g. 15% for grades 1 and 2 in posterior circulation aneurysms operated acutely, but 19% overall for all grades.

A recent multicentre prospective randomised study examining the prevention of vasospasm with cisternal rTPA⁴, showed a 3 month mortality of 19% and a good outcome in only 50% of patients with severe SAH operated within 48 hours of the haemorrhage (some of these patients were Grade 5). Three patients rebled between 14 days and 3 months after surgery. This emphasises the still serious outcome in the condition even with modern surgical management techniques in large centres.

Endovascular techniques for the treatment of intracranial aneurysms have been evolving over the past 10 to 15 years. The Guglielmi Detachable Coil device (GDC) has been in use in Europe since 1992 and in North America since 1991 and is a major technical advance. Recent data from the USA multicentre assessment⁶ of the GDC device prior to FDA approval showed a complication rate similar or even better than conventional neurosurgery in a selected high surgical risk group. The GDC device has been used in approximately 4,000 patients world-wide. It has significantly improved endovascular treatment by providing a

technically safer and more reliable coiling system.

Early clinical results with this device in the posterior circulation were published in 1992⁵ and a review of the multi-centre North American experience in the first 1,058 patients has been presented by senior investigators of this system⁶. Data from the clinical co-ordinating centre, and unpublished results from other centres with significant endovascular experience suggest complication rates of aneurysm treatment following SAH, appear to be in the range of 1.5-5% mortality and 3-5% morbidity⁷. Observed rebleeding rates are less than 1% of treated patients. The patient selection in these series have tended to be patients with more difficult surgical aneurysms, larger size, patients in poorer clinical grade and with a high proportion of posterior circulation aneurysms.

An editorial in *Journal of Neurosurgery*⁸, reviewed the current situation and whilst recognising potential limitations, advocated the development of protocols for a randomised trial comparing endovascular treatment with neurosurgery.

Mission statement

The *International Subarachnoid Aneurysm Trial* (ISAT), is the first and currently only large, multicentre prospective randomised trial of surgery compared with endovascular coil treatment of acute subarachnoid haemorrhage in the world. It aims to recruit up to 3,000 patients in about 25 centres in four years. This will produce the largest ever prospective randomised study in aneurysmal subarachnoid haemorrhage management. The clinical ramifications and impact on healthcare costs will be of major significance if substantial differences are found in the outcome according to randomised procedure.

The value of ISAT to health policy and practice

In the past new surgical techniques and minimally invasive surgery have rarely been subjected to randomised trials. There have been no randomised trials in the surgical management of subarachnoid haemorrhage since McKissock's⁹ series of studies in the 1960's of conservative versus surgical management because no satisfactory alternative method of treating ruptured intracranial aneurysms was available.

The endovascular technique which has recently been developed has gained rapid acceptance in some countries, France in particular, where it is being used as the procedure of choice for ruptured aneurysms in some centres. It is essential that the technique is tested in a systematic manner before it becomes regarded as standard practice for what would otherwise be "surgical aneurysms". Currently in most centres the technique is used in patients with surgically difficult aneurysms or in patients not suitable for surgery on grounds of clinical condition, age or medical problems¹⁰. The endovascular techniques are usually performed by specialised neuroradiologists with a particular skill and experience in endovascular techniques.

Cost implications and economic evaluation

Many patients presenting with SAH do so in the 30-60 age group, and were previously completely well and fully economically active. The consequences of the haemorrhage to the patient and family may be devastating. It is probable that differences in outcome will affect costs incurred by patients and their carers, in particular - return to work. In addition, there are significant differences in the hardware and consumable costs of endovascular treatment of ruptured intracranial aneurysms compared with the hardware and consumables for conventional neurosurgical treatment: the cost of the coils and catheters used in endovascular treatment of a typical surgical aneurysm in the U.K. is approximately £2,000 - £2,500, whereas consumables and clips for a surgical clipping are approximately £300. However, overall care costs of these procedures are not available, and it is not known to what extent the overall costs may be affected by differences in other costs relating to length of stay in intensive therapy units or overall time in hospital. Finally, net costs of the two procedures may be influenced by differences in rebleeding rates, neuropsychological, psychosocial problems, or other complications. The differences in the direct and indirect costs associated with each treatment are likely to be of major interest to patients, clinicians, researchers, managers and purchasers. The only way in which differences can accurately be measured is within the context of a randomised controlled trial. For these reasons, there are compelling grounds for systematically examining costs in this trial, with the objective of assembling reliable data on:

- i. the net direct costs to the health sector associated with each procedure
- ii. the net indirect costs to patients and their families

It is appropriate that quality of life should also be incorporated in the economic evaluation, alongside the modified Rankin, the Glasgow Outcome Scale and the other instruments being used in the trial to assess morbidity. The EUROQOL¹¹ instrument, involving a simple 5-question questionnaire to give health states available from a large population based study, has these characteristics. It is proposed to administer EUROQOL by post at 12 months.

Statistical methods

a. Sample size and power calculations

Data from the pilot phase of the study suggests that by about two months (and similarly at one year) between 75 and 80% of patients are in Rankin¹⁵ grades 1 and 2 (based on 95 patients at two months). It may be expected there will be some further improvement by one year.

Therefore an assumption that 80% of the randomised population reach Rankin 1 or 2 is realistic.

Assuming that between 20 and 25% of the patients randomised to surgery do not reach Rankin 1 or 2 by one year the number of patients required in the study to attain an alpha level of 0.05 and 0.01 for 20 and 25% difference between the groups are as follows:

Rankin 3-6 @ 1 year		α	Power	n	Expected No. of events
Surgical	Endovascular				
20%	15%	0.05	80%	1802	315
			90%	2414	425
		0.01	80%	2648	463
			90%	3416	598
25%	19%	0.05	80%	1490	328
			90%	1996	439
		0.01	80%	2218	488
			90%	2813	619
30%	22.5%	0.05	80%	1076	282
			90%	1440	378
		0.01	80%	1600	420
			90%	2040	536
30%	24%	0.05	80%	1720	464
			90%	2300	621
		0.01	80%	2550	688
			90%	3250	877

b. Statistical analysis

The timing and planning of the analysis of the trial will be agreed between the trial statistician, the data monitoring committee and the MRC statistician. The stopping rules and plan for interim analysis will be decided by the DMC in liaison with the trial steering committee. The TSC has requested a review of recruitment and interim analysis at 18 months into the main study to determine whether the primary objective of the trial can be achieved.

c. Publication policy

Any announcement or publication of results and publicity concerning the trial will require approval of the trial steering committee. Such publications will be in the names of all the investigators in the participating centres unless they represent a specific subset of results concerning the trial e.g. health economics or neuropsychology.

Definitions of Outcome Scales used in the ISAT trial and methods of collection

The World Federation of Neurological Surgeons has adopted the Glasgow Outcome Scale¹⁴ as the standard outcome measure for the collection of data on SAH management.

The Glasgow Outcome Scale¹⁴ (GOS) grading system is recognised as being relatively crude and there is a large step between the original definition of grade 2 and 3 on this scale. The techniques and the methods of collection are not always detailed or validated in the literature.

For the purposes of this study GOS 1 and 2 will be used as equivalent to Rankin^{15 16} 1 and 2 respectively. The outcome grade will be defined by the patients response to question 14 in the follow- up questionnaire and used as the equivalent of the Rankin scale as defined below.

Rankin 3 and 4 will be categorised as GOS 3.

Modified Rankin or Oxford Handicap Scale (OHS) splits Rankin 1 into two grades – 0 and 1.

This will also be collected from the patients response to question 14 in the the follow-up questionnaire. (see below).

Patients ticking the first or second boxes will be categorised as modified Rankin 0 or 1 and GOS 1. Patients ticking the third box will be categorised as Rankin 2 and GOS 2. Other ticks will be categorised in a lower GOS and Rankin grade.

These responses will be validated blind against an independent assessment of outcome grades by the neuropsychologist obtained at the time of neuropsychology assessment in a sample of patients at one year.

<i>Tick below</i>		<i>Office use only</i>	
		OHS	GOS
	I have no symptoms at all and cope well with life.	0	1
	I have a few symptoms but these do not interfere with my everyday life.	1	1
	I have symptoms which have caused some changes in my life but I am still able to look after myself.	2	2
	I have symptoms which have significantly changed my life and prevent me from coping fully, and I need some help looking after myself.	3	3
	I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night.	4	3
	I have major symptoms which severely handicap me and I need constant attention day and night.	5	4

Angiographic evaluation and outcome

Angiographic data will be collected on all patients in this study.

Whilst the primary and secondary end points are deliberately clinical, the angiographic outcomes will be available for analysis and the relationship between the angiographic findings and any rebleeding will be analysed.

Aims and Objectives

Aim

To compare the safety and efficacy of an endovascular treatment policy of ruptured intracranial aneurysms with a conventional neurosurgical treatment policy in an eligible population.

Design

An open, randomised, controlled clinical trial of patients with acute subarachnoid haemorrhage admitted to participating centres in whom the responsible doctor is uncertain whether endovascular or neurosurgical treatment policy is best for that patient.

Randomisation to endovascular or neurosurgical treatment policy via a 24-hour telephone service provided by the clinical trials services unit at the co-ordinating centre.

Primary objective

To determine whether an endovascular treatment policy of acutely ruptured intracranial aneurysms compared with a neurosurgical treatment policy, reduces the proportion of patients with a moderate or poor outcome (defined by Rankin grade 3-6) by 25% at one year.

Secondary objective

To determine whether endovascular treatment:

- is as effective as neurosurgery in preventing re-bleeding from the treated aneurysm
- results in a better quality of life than neurosurgery at one year (Euroqol measure)
- is more cost effective than neurosurgical treatment
- improves the neuropsychological outcome at one year (some centres only)

Tertiary objective

- To examine the longer term outcome over five years with specific reference to re-bleed rates.
- To determine the long-term significance of angiographic results.

Entry criteria for randomisation

1. Proven subarachnoid haemorrhage on CT or lumbar puncture.
2. Presence of an intracranial aneurysm demonstrated by **intra-arterial angiography** likely to be responsible for the subarachnoid haemorrhage.
3. The patient is in a clinical state that justifies treatment at some time by either surgical or endovascular means. WFNS Grade 5 patients may be included. Patients in whom the assessment of grade is impossible (e.g. paralysed and ventilated from the ictus) may be included.
4. Intracranial aneurysm judged to be suitable for either technique based on its angiographic anatomy and the responsible clinician **is uncertain** which is the best method of treatment.
5. Appropriate consent of the patient or relatives.

Exclusion criteria

1. Most recent subarachnoid haemorrhage more than 28 days prior to randomisation.
2. Participation in another randomised drug or clinical trial for subarachnoid haemorrhage.
3. SAH not proven on CT or lumbar puncture.
4. Patient is regarded as not suitable for both treatments.
5. Refusal of consent.
6. Target aneurysm is not angiographically proven on intra-arterial angiography.
7. The target aneurysm is unruptured.

Grade 5 patients

The Executive and Steering committees have considered the issues of Grade 5 patients and decided that they may be included in the trial where clinical uncertainty is judged to exist

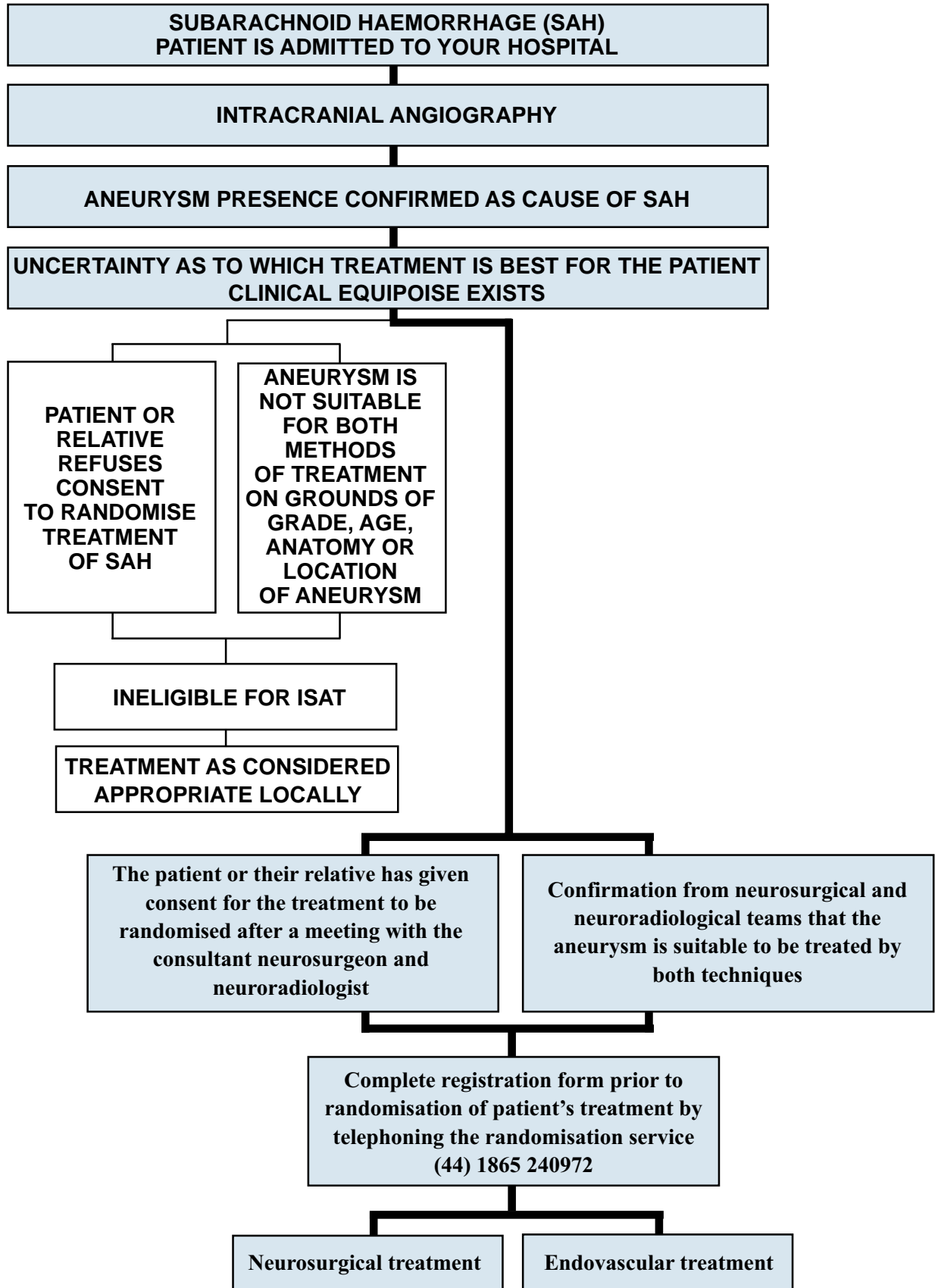
The main analysis will be carried out with this group of patients. A separate sensitivity analysis will also be conducted.

ISAT treatment plan

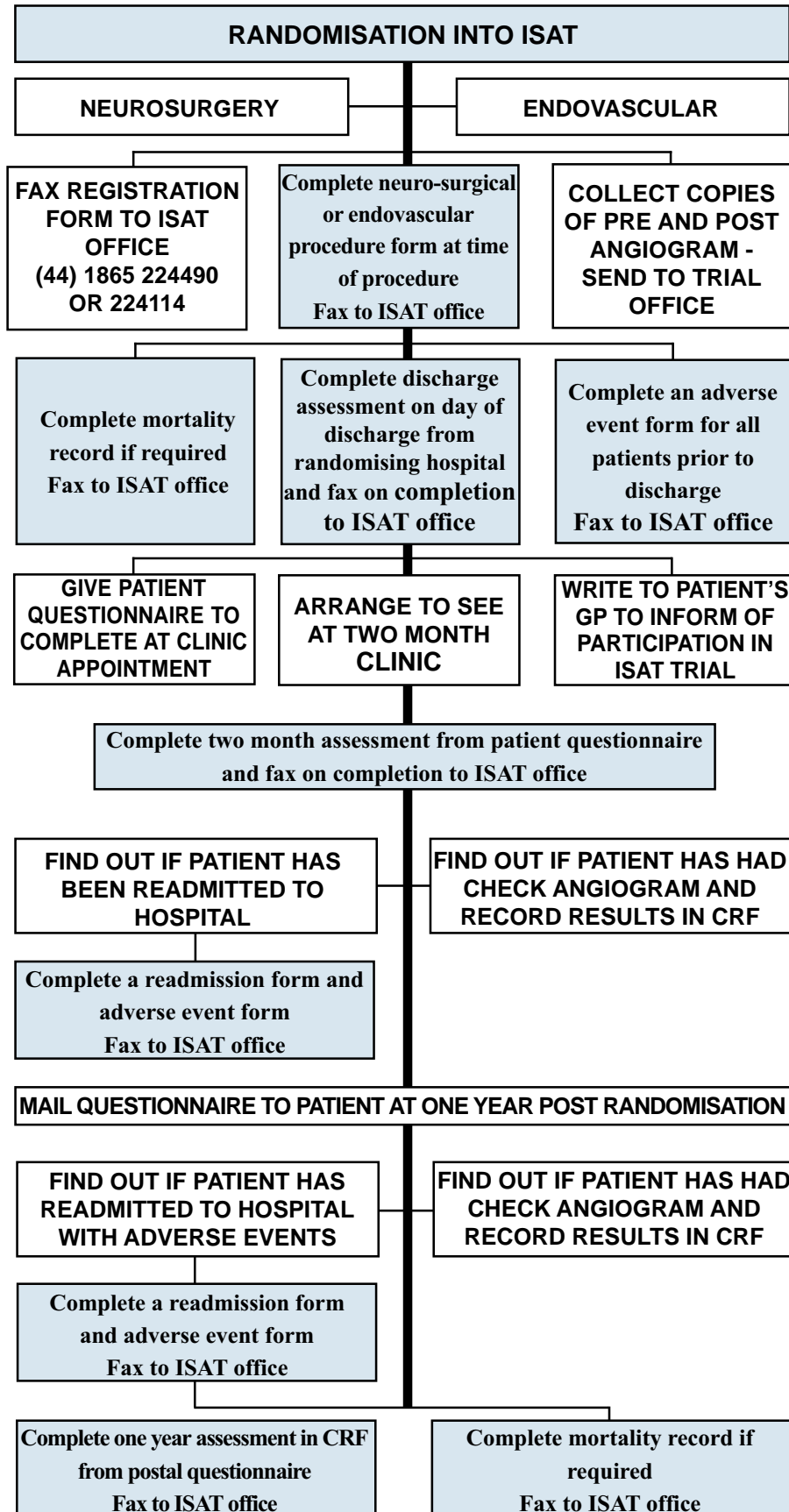
1. **Confirmation of subarachnoid haemorrhage** by CT scan or lumbar puncture.
2. **Admission** to neurosurgery or neurology ward for treatment.
3. Baseline **neurological evaluation** with recording of WFNS grading.
4. Diagnostic intra-arterial cerebral **angiography**.
5. The patient will be eligible for randomisation if they have a **confirmed aneurysm** likely to be responsible for the SAH where there is **uncertainty** over the best method of treatment.
6. Appropriate **consent** of patient or relatives to treatment and entry into the trial in line with the local ethical or human research board approval and policy.
7. **Randomisation** by a telephone call to the central randomisation office after completion of the registration form, the treatment allocated will be notified immediately by the telephone operator.
8. The **timing of surgery or endovascular treatment** will be decided by the consultant neurosurgeon or neuroradiologist in charge of the case.
9. **Procedure form** completed following the treatment. This will also record the name and grade of the operating surgeon/interventionist.
10. **Post operative intra-arterial angiography** is required in the surgical patients at some time unless it is felt to be contraindicated by the surgeon in charge. This may be carried out before patient discharge.
11. Any **other interventions** which may be felt clinically appropriate may be used in either patient group, such as shunting, haematoma evacuation, hypertensive or other therapy for vasospasm. This should be recorded on the discharge or subsequent procedure form. Major adverse events should be recorded on the **adverse events form**.
12. **Assessment at discharge** by the local trial co-ordinator recording key data concerning the patient including the WFNS grade at time of discharge from neurosurgical unit, lengths of stay, adverse events and ITU time.
13. **Clinical follow up** in accordance with the routine of the neurosurgical department concerned.
14. **Angiogram copies** will be collected centrally. Pre and Post treatment angiograms will be collected and available for analysis. Sample images from any subsequent check angiogram will be collected. (A separate protocol for the angiogram sub-study will be issued at a later date.)

15. **Two month follow-up** patient questionnaire will be handed or mailed to the patient by the local co-ordinator. This is to establish early outcome data. Outcome assessment will be collected on the Glasgow Outcome Scale, the Rankin Scale, the Oxford Handicap Scale and Euroqol. Normally this assessment can be done at the time of the patient's routine hospital outpatient appointment following treatment of the aneurysm. This will be returned to the local trial co-ordinator who will then complete the case record form and fax a copy of the assessment immediately to the trial head office.
16. **Follow-up intra-arterial angiography** will be performed in endovascularly-treated patients at approximately six months after treatment. It may be performed at other intervals if considered appropriate.
17. **Neuropsychological assessment** will be made at one year in some centres.
18. **One year follow-up** will be conducted by mailing of a postal questionnaire to known surviving patients and relatives at one year after randomisation. This may be carried out from the central co-ordinating office if preferred by the participating centre. These questionnaires will collect Glasgow Outcome Scale, Rankin, Oxford Handicap scale and Euroqol. If these are not received within one month the relevant national or local co-ordinator will be notified and asked to obtain follow-up of what has happened and obtain completed forms and the patient status.
19. **Annual follow-up for at least five years** by annual telephone contact with General Practitioner and/or patient in the UK, primary physician, patient or next of kin in other countries as appropriate. GP notes will be flagged to request notification of any major events or re-bleeds.
20. In the event of a patient's readmission, the **hospital readmission form** must be completed.
21. In the event of an **adverse event** related to the subarachnoid haemorrhage (during or after the original admission) an **adverse event and additional procedure form** should be completed.
22. **Long term follow-up** for mortality by flagging of patients with OPCS or equivalent in other countries where this is available. This will be done by the central co-ordinating office, but necessitates the collection of flagging data locally.
23. In the case of deaths details of cause and a copy of death certificate should be obtained and autopsy data recorded, on the **mortality report**.

ISAT TRIAL PRE-RANDOMISATION CHART



ISAT TRIAL POST RANDOMISATION CHART



Centre requirements

1. The centre must be a neurosurgical centre that is treating a significant number of patients with acute SAH. It should have a referral base of at least 1.5 million and **preferably** it should be a primary referral centre for patients with this disease rather than a tertiary referral centre.
2. There must be good vascular neurosurgical expertise with regular experience of aneurysm clipping.
3. The names and grades of ‘operators’ in each centre should be submitted to the ISAT office. The years of expertise of aneurysm surgery or number of aneurysms treated should be listed for each operator. This will be maintained in a confidential centre log.
4. The centre must identify a local trial co-ordinator who will be responsible for all the data collection at the centre concerned. It is most appropriate that this is an experienced nurse or radiographer, this nominated person will also be responsible for ensuring maintenance of the ascertainment log in the angiogram room. A monthly return will be expected to the trial office.
5. The approval of the local ethical committee must be obtained and copies of the ethical approval (Human Research Approval) and any appropriate indemnity must be lodged with the trial office.
6. There must be at least one experienced endovascular operator. It is desirable to have more than one experienced operator. Where there is only one operator, if he/she is not available to treat a patient who is suitable for entry into the trial, that patient **must not** be randomised as early treatment at an appropriate time may not be possible.
7. The endovascular operator must have wide interventional neuroradiological experience and must have treated at least 30 cases with the Guglielmi detachable coil device before randomising patients in the trial.
8. The **only device** that may be used in trial patients **at this time** is the **Guglielmi detachable coil (GDC)** device. It will be up to the trial steering committee to decide if any other device may be used in future. Such a decision would be based on safety and efficacy data submitted to the steering committee by either the manufacturer or interventionalist. Any device used **must** have the approval of the relevant regulatory authority in the country concerned.
9. All treatment must be performed on modern digital angiographic equipment with a 1024 matrix.

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Dr Richard Scott, Neuropsychologist, Russell Cairns Unit, Radcliffe Infirmary

Professor Martin P. Vessey, Public Health Medicine, University of Oxford

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