17th June 1999

Protocol for EndoVascular Aneurysm Repair (EVAR) Trials

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Summary

Training centres for the use of endovascular stent grafts for abdominal aortic aneurysm (AAA) repair will be established and progress audited in a National Society Registry. Trial co-ordinators at initially 13 UK centres will be trained at Charing Cross Hospital in correct protocol procedures and collection of health related quality of life (HRQL). Trained operators will enter patients undergoing AAA repair into randomised trials of (1) EVAR vs. Open repair (OR) in fit patients and (2) EVAR plus best medical treatment vs. best medical treatment in patients unfit for OR. Each trial will compare EVAR against current best alternative in terms of mortality, durability, safety and costs as well as generic and patient specific health related quality of life (HRQL). 1100 patients will be entered over 4 yrs, 800 in trial 1 and 300 in trial 2.

1. Benefits the proposed investigation will bring to the NHS

The investigation will support the findings of the Joint Working Party for the Vascular Surgical Society of Great Britain & Ireland (VSS) and the British Society of Interventional Radiologists (BSIR), to bring the disciplines together for the introduction of endovascular grafting of abdominal aortic aneurysm and maintain the Registry of Endovascular Treatment of Aneurysms (RETA) which was initiated on the 1st January 1996 by Mr Jonathan Beard of the Sheffield Vascular Institute. Centres will be provided in Nottingham, Leicester, Liverpool and Newcastle to train surgeons and radiologists together (the operators) according to the VSS and BSIR Guidelines. Trainee learning will be by open audit (RETA) with feedback and provide a model for future surgical and interventional radiological technology assessment during development. Learning curves of both operators and newly introduced stent graft systems can be thus checked before introduction. Currently, trainers are finding that approximately 20 EVAR procedures are needed for training the surgeon and radiologist working together. Trial findings will indicate degree of safety, efficacy and durability of new EVAR systems as they are introduced and in fit patients to establish the value of EVAR against conventional abdominal aortic aneurysm (AAA) open repair (OR) with respect to mortality, durability, safety, costs, and quality of life. The investigation should also show if EVAR has any place in the management of patients with AAA unfit for conventional open repair (OR). Findings could markedly reduce the costs for treatment of all AAAs and provide potential to reduce bed occupancy and increase patient satisfaction. A Cochrane Review will be initiated.

2. Background to the project.

The incidence of abdominal aortic aneurysm in England and Wales has been increasing. From 1950 to 1984 age standardised mortality rose twenty fold in men to 47.1 per 100,000 population and eleven fold in women to 22.2 per 100,000[1]. The authors concluded that the trends were not wholly compatible with increases in diagnosis and surgery because there were inconsistencies by age and sex and increases had occurred in the number of complicated as well as uncomplicated cases. Similarities to the trends were noted in North America, elsewhere in Europe and Australasia and so the authors concluded that there was a true increase in the incidence of abdominal aortic aneurysms. At the beginning of this decade Parodi, Palmaz and Barone in Argentina[2] and Volodos in the Ukraine introduced EVAR in sicker patients with shorter hospital stay. These pioneers used hand made stent graft systems beginning with a repair to lie entirely within the abdominal aorta (aorto-aortic graft). Subsequently it has been shown that the aorto-aortic EVAR can be used in less than 10% of patients and bifurcation systems have been developed which enable approximately 25% of AAA to be managed by an EVAR method[3]. "Home-made systems" have been introduced in this country in Nottingham[4] and Leicester[5]. These systems have employed an aorto uni iliac EVAR system. The second side is occluded using a Dacron sac and stent and the procedure completed with a femoro femoral crossover graft just leaving the patient with 2 small incisions in the groins and minimum pain. The Nottingham group[4] have shown recently that using their system, 75% of all AAA could be managed by EVAR.

The applicants are ideally placed to carry out the proposed research for a number of reasons. The MRC supported multicentre Femoropopliteal Bypass Trial and UK Small AAA Trial[6] have given valuable experience in multi-centre vascular surgical trials in Britain. There is an excellent network of collaboration in vascular surgery in Britain and the applicants are well placed in the VSS (Bell, President Elect 1999, Greenhalgh, President Elect 2000). The collaboration extends through the joint working party to the officers of the BSIR (President 1999 Professor A. Adam). Such national collaboration is no better established in any other country at present but other European countries will be encouraged to copy our trial protocols with a view to the possible pooling of data. There is also interest in Canada and Australia to enter patients into our trial. The applicants have demonstrated their ability in the UK Small AAA Trial to recruit according to schedule, document carefully and achieve a result (published in The Lancet November 1998). Facilities are in place to assess costs (Brunel) and Health Related Quality of Life (York). The UK Small AAA Trial has indicated that we can expect to recruit about 1000 patients fit for conventional surgery (OR) over 4 years and during that time approximately 70 patients per annum will be seen with AAA who are unfit for OR. Outside the UK small AAA trial, patients deemed unfit for surgery had a 22% mortality at 10 months (vide infra) and 50% mortality at 2 years with best medical treatment.

2.1 The Registry for Endovascular Treatment of Aneurysms (RETA)

The National RETA registry was initiated in January 1996 to audit "home-made" and commercially available EVAR systems deployed within the UK. Annual audits have been conducted and reports are available to the EVAR Trial Management Committee, principally to be advised when centres are trained.

According to the 1998 data, patients have been classified as either fit or unfit for open repair (OR). The proportions of each are given in Figure 1 and represent the distribution of patients that would enter EVAR Trial 1 (fit for OR) or EVAR Trial 2 (unfit for OR). It is clear that the operative mortality at 30 days is significantly worse for unfit patients ($\chi^2 = 23.4$, $p < 0.001$).

In patients suitable for open repair the data for 1996, 1997 and 1998 (Figure 2) show decreasing 30 day mortality. It must be remembered that not all EVAR procedures in the UK are recorded in these data.

EVAR is currently being used both for fit for OR patients (75%) and unfit for OR patients (25%). Consequently it is appropriate to pose the question of the original NHS R&D HTA commissioning brief **what is the cost effectiveness of aortic stenting -v- other innovative methods -v- OR for elective AAA's?** Currently the accepted alternative to EVAR is open repair (OR) in patients who are fit enough for the procedure. For those that are not fit for OR, EVAR is currently being used as an adjunct to best medical treatment. Should it be? Can best medical treatment be "innovative"? We have shown that smoking increases the growth rate of small abdominal aortic aneurysms[7] and so after EVAR one can no longer expect the aortic dimensions proximal and distal to the stents to remain constant if a patient continues to smoke. Consequently innovative best medical treatment could involve the setting up of smoking advice clinics using nicotine replacement therapy in the trial centres with measurement of smoking markers for compliance. Careful control of blood pressure including reduction in pulse pressure should be advocated. EVAR procedures are being performed in the UK on patients less than fit for OR and this is a potentially expensive exercise for the NHS and the appropriate trial would be to assess any adjuvant benefit of EVAR beyond current best medical practice, particularly any treatment which can slow the expansion of the aortic aneurysm.

In considering a random allocation trial EVAR v OR, it is argued that the operative mortality for the commercially available stent grafts is very low. Blum et al in Freiburg, Germany using the Mintek System in 140 patients, reported a 0.7% 30d mortality[8]. Moore *et. al*[9] in North America reported a 33% 30d mortality in 30 patients using another commercially available device. The Eurostar Audit of Systems in Europe has data on 400 procedures with a 30d mortality of 4% for mainly commercially available systems[10]. Presently commercially

available systems can only be used in up to 25% of AAA and generally in the less diseased or extensive AAA with suitable anatomical dimensions. We had no alternative but to base our calculations on the pilot data of RETA which included aorto-uni iliac data of "home-made systems" which brings to 75% the proportion of patients correctable by EVAR[11].

2.2 The UK Small Aneurysm Trial

The results of The UK Small Aneurysm Trial were reported in two back-to-back papers published in *The Lancet* on November 21st 1998[6]. During the 4 years of recruitment from August 1991 to 1995, 1090 patients aged 60 to 76 presenting with asymptomatic, infrarenal AAA sized between 4.0 and 5.5cm were randomised either to regular ultrasound surveillance or elective open repair. Patients were followed for a further 3 years in terms of mortality, cost effectiveness and health related quality of life. Kaplan-Meier survival analysis indicated that surgical intervention for abdominal aortic aneurysm was not justified in terms of all-cause mortality, cost effectiveness or health related quality of life. Survival was similar in both groups and regular surveillance was found to be a safe and reliable mode of treatment to monitor the aneurysm until it grew to 5.5cm, became tender, grew fast (>1.0cm/year) or ruptured. The 30 day operative mortality for patients randomised to elective surgery in the UK Small Aneurysm Trial was 5.8% and an annual rupture rate of 1% was found. Accordingly, no benefit was found for early surgical intervention (within 3 months of randomisation for AAA 4.0 – 5.5cm). Instead, surveillance to 5.5cm was seen to be better. We see no reason to modify these findings for EVAR at this stage and AAA $\geq$ 5.5cm will be considered for surgery. From the Freeman Hospital, Newcastle, Berridge et al reported a 5 year prospective audit on 1,131 patients undergoing surgery for AAA from 1988 to 1992[12]. The teaching hospital 30d mortality was 3.9% and DGH mortality 12.0%. The audit showed a far greater mortality for over 80 year olds (23.8%), compared with under 80 (7.6%). Hopkinson in Nottingham has also found higher mortality in >85 year old patients undergoing EVAR[11].

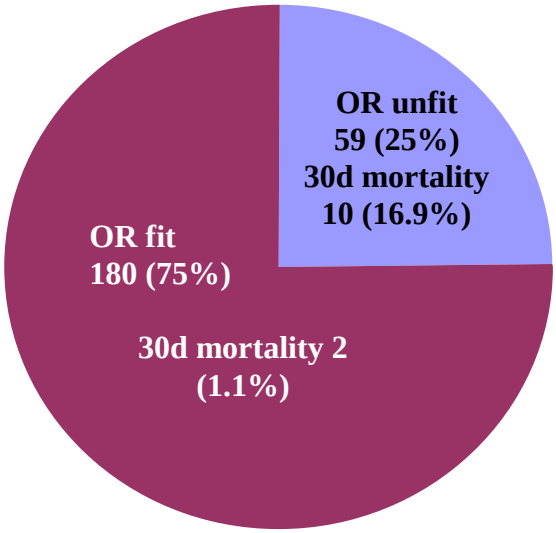


Figure 1 – RETA data for 30 day EVAR mortality (1998) according to fitness for Open Repair (OR), (n=239)

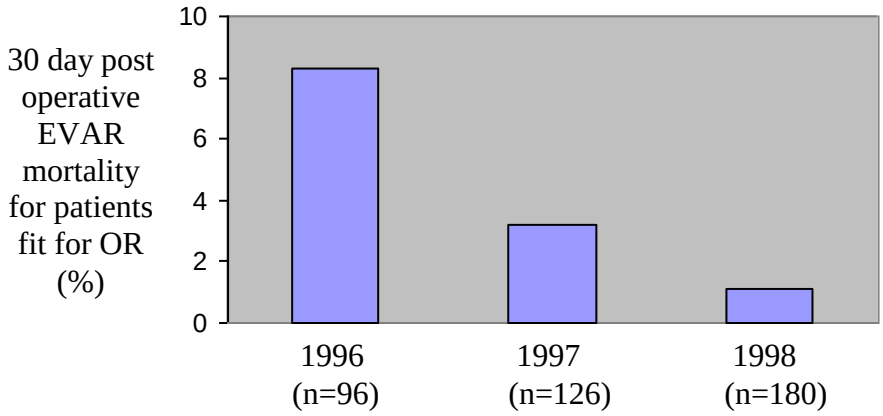


Figure 2 – 30 day post operative mortality for patients classified as fit for open repair (OR)
Data taken from RETA annual reports from 1996 to 1998.
(n=number of EVARS performed in that year)

3. Plan of investigation including research methodology proposed

3.1 Trial Management Structure

Data Monitoring & Ethics Committee (DMEC)

This has been convened by Professor Philip Poole-Wilson, (Professor of Cardiology, National Heart & Lung Institute, Brompton Hospital) who has kindly agreed to chair the DMEC. Membership includes 2 representatives of The Vascular Surgical Society of Great Britain & Ireland (VSSGBI), namely Professor CV Ruckley (Edinburgh) and Mr WB Campbell (Exeter) and also 2 representatives of The British Society of Interventional Radiology (BSIR), namely Dr MRE Dean (Shrewsbury) and Dr MST Ruttley (Cardiff) as agreed with their councils. Dr EC Coles (Cardiff) has agreed to act as the statistical representative for DMEC. The DMEC will communicate with the Trial Steering Committee (TSC). The DMEC and Trial Management Committee (TMC) will together discuss stopping rules. Audit of the data is "closed" as well as being device, operator and centre specific. Information from EVAR procedures elsewhere may be fed into the DMEC and the manufacturer will be able to feed in details of product modification. The DMEC may wish to meet EVAR manufacturers from time to time as an EVAR comparative audit will be performed as subgroup analyses by DMEC (TRACKER TRIALS).

Trial Steering Committee (TSC)

This will meet as required. Professor Richard Lilford has accepted the chair. The TSC would include Roger Greenhalgh for the applicants and Trial Management Committee. Surgical and radiological input will be supplied by the operators at the participating centres who will serve on the TSC on an annual rotation basis. There should be patient representation on this committee which will receive constant input from the DMEC and TMC. It is expected that patient representation will involve participation from patients treated with both open repair and EVAR.

Trial Management Committee (TMC)

This is concerned with the day to day running of the EVAR trials and relates to both the DMEC and Trial Steering Committee. It will be chaired by Roger Greenhalgh and includes Simon Thompson (statistics), Ian Russell (HRQL), Jonathan Beard (RETA), Janet Powell (best medical), Martin Buxton (costs). There is also one participating surgeon and radiologist or representatives of them who serve on this committee on an annual rotation basis. The committee is convened by Louise Brown.

Regional Trial Participants Committee (RTPC)

This includes a surgical and radiological representative of each participating centre and is convened by Louise Brown as required and requested by trial centres, training centres and the trial co-ordinating centre whenever the need arises but usually at annual meetings such as the VSS and BSIR.

3.2 The training of surgeons and radiologists (operators) and trial co-ordinators

Surgeons and interventional radiologists (Operators) will be trained in Nottingham (Hopkinson) and Leicester (Bell) for home-made aorto-uni iliac systems. Training for the commercially available 'Vanguard' bifurcation system (Boston Scientific) will be in Liverpool (Harris) and Newcastle (Wyatt). In addition Gough (Leeds) has offered training for the Endovascular Technology (EVT) device and Adiseshiah (UCL) could train for the World Medical Talent Graft. In addition to the six training centres mentioned, and the National Registry (RETA) in Sheffield and the Trial Co-ordinating Centre in London (Charing Cross), the following centres are trained and have agreed to take part in the trial:- Bournemouth (Parvin), Guy's (Taylor), Hull (Wilkinson), Manchester Royal (Walker), Manchester Withington (McCollum). Other centres can come on stream when trained and will submit experience to Sheffield.

The success of the new technique is thought to be highly device, operator and centre dependant and therefore hospitals need to demonstrate competence at performing the new procedure before it can realistically compete with current alternative best medical or surgical practice. Trial co-ordinators at centres entering patients will be trained before the first patient is entered and skills will be checked during the trial and compared between centres.

3.3 Role of supporting hospitals

It is important that patient recruitment is as high as possible. Each trained regional centre also acts as a specialist centre in its own area. It may be possible for surrounding non-vascular specialist hospitals to support recruitment by referring vascular patients believed to be suitable for the EVAR Trials to that regional centre. If anatomically suitable for EVAR and agreeable to randomisation the patient receives treatment at the regional centre. Thus <u>all</u> EVAR, OR, best medical treatment and follow-up is performed at the regional centre.

3.4 Generalizability

It is of particular importance that patients found to be unsuitable for an EVAR device are recorded at initial consultation. Numbers of unsuitable patients and reasons for this will determine what proportion of AAA patients are anatomically suitable for an EVAR device at the national level. It is thought that certain centres, eg. Liverpool, Leicester, Sheffield and Bournemouth act as both the "DGH" and "regional centre" for their area. These centres could be ideal for assessing generalizability according to postcode of patient being treated. These centres could give more reliable population information about the proportion of patients across the land who could be treated by EVAR.

3.5 Entry Criteria

a) Age at least 60 years

A minimum age of 60 years is chosen as surgeons may wish to manage patients under 60 years in a different way because frequently there is an associated genetic cause where expansion rates and extent of AAA may be extreme, such as Marfan syndrome. No upper age limit is thought necessary as very elderly patients may benefit from the use of an EVAR device and their recruitment will be important for achieving the numbers required.

b) Size of AAA

The criterion for entry into both trials is an AAA diameter measuring $\geq$ 5.5cm according to a CT scan. The UK Small Aneurysm Trial has shown that it is safe to leave abdominal aortic aneurysms until they reach this size. However, reproducibility differences between Duplex Ultrasound and CT scanners can lead to significant variation in AAA diameters. Duplex scanning tends to produce AAA diameters smaller than CT scanning and therefore we recommend that patients presenting with a $\geq$ 5.0cm AAA on Duplex should be sent for a CT scan to determine whether the AAA is $\geq$5.5cm in any diameter on CT scan and thus suitable for EVAR Trial entry. Tender AAA and contained ruptures may be included provided the AAA measures at least 5.5cm on a CT scan and suitable EVAR equipment is available at such short notice. Tender AAA < 5.5cm requiring surgery will only have the options of open repair or surveillance.

c) Anatomical suitability for EVAR

This is assessed usually by spiral CT or conventional CT combined with conventional angiography with a marked catheter to enable the calculation of length. The training centres differ in their methods of measuring the tortuous length of the abdominal aorta. This measurement is extremely important in calculating the precise length of the EVAR system used. The learning curve of every operator indicates that there is a repeated tendency for a graft system to be chosen too short. A surgeon is used to fixing the upper end at open repair and cutting the prosthetic graft to length before fixing the lower end. With EVAR the lengths must be carefully measured in the pre-operative period and even then errors can occur. The precise measurement particularly of the axial length of the aneurysm is critical for good results. The trial centre radiologist will require special training in these calculations which will be checked at training centres and by the commercial companies involved until proficiency is achieved. The trial co-ordinator must work closely with the local radiologist and appropriate training centre and document how the AAA was assessed and how the size and type of EVAR device was selected.

Patients found to be unsuitable for an EVAR device are not flagged for mortality at The Office of National Statistics (ONS) but reasons for unsuitability are collected. Patients referred from supporting hospitals are returned there for treatment.

d) Fitness for Surgery

This is determined locally by the surgeon, radiologist, anaesthetist and cardiologist. It was originally thought that ASA grades I, II and III would indicate entry to EVAR Trial 1 and ASA IV patients would permit entry into EVAR Trial 2. However, despite the simplicity of ASA grade it can be open to different interpretation at each centre and has proved too difficult to use as a classification system for EVAR Trial 1 or 2. Recently, more sophisticated tests have not been good predictors of outcome in vascular surgery[13]. It has been appreciated during the UK Small Aneurysm Trial that fitness "inflation" has emerged with respect to the size of aneurysm. Patients who were earlier described as "unfit for OR" and later developed a larger aneurysm were suddenly deemed "fit for the procedure". This could equally happen for these current trials. For the purposes of pragmatism, fitness is determined at the local level for these trials. Recommended guidelines on cardiac, respiratory and renal status have been provided as outlined in Figure 3 and baseline data will be used to assess fitness of randomised patients at the final analysis. These guidelines may help provide some conformity of fitness classification for EVAR Trial 1 or 2.

Recommended guidelines for assessment of patient fitness for open repair and suitability for EVAR Trial 1 or 2

Patient fitness for open repair is decided at the local level, however, these guidelines may provide some assistance.

Cardiac status

Normally, patients presenting with the following cardiac symptoms would not be recommended for any surgical intervention:

- MI within last 3 months
- Onset of angina within the last 3 months
- Unstable angina at night or at rest

Normally, patients presenting with the following symptoms would be unsuitable for open repair (EVAR Trial 1) but may be suitable for EVAR Trial 2:

- Severe valve disease
- Significant arrhythmia
- Uncontrolled congestive cardiac failure

Respiratory status (no constraints for EVAR Trial 2)

Open repair (EVAR Trial 1) would not be recommended for patients presenting with the following respiratory symptoms:

- Unable to walk up a flight of stairs without shortness of breath (even if there is some angina on effort).
- $FEV_1 < 1.0$ L
- $PO_2 < 8.0$ KPa
- $PCO_2 > 6.5$ KPa

Renal status (no constraints for EVAR Trial 2)

Open repair might not be recommended for patients presenting with serum creatinine levels greater than 200μmol/L. These patients may be suitable for EVAR Trial 2.

Figure 3

e) Randomisation

This is performed at Charing Cross, where randomisation tables have been produced using the STATA 6.0 statistical package. Randomisation is stratified by centre.

Trial 1

Consideration has been given to whether we should seek patient preference but the majority view is that trialists are truly uncertain of whether OR or EVAR is preferable for patients short term or long term and so the equipoise position will exist from which randomisation to OR or EVAR can occur. We aim not to introduce the matter of patient preference but hope for maximum recruitment into 50:50 random allocation. However if patient preference emerges we shall respect it and note outcomes. It is our understanding that the EVAR device is currently not available on the NHS except as part of these randomised controlled trials. We feel that on balance, if we introduce the concept of patient preference, this could lose randomised numbers and tend to bias patients when in fact trialists truly do not know which procedure is better.

Trial 2

For the OR unfit group the ethical considerations are more difficult. The trialists are inclined to pursue a randomised trial here because we are being pressed to use EVAR in these patients. Randomisation should be between EVAR and best medical treatment against best medical treatment alone. Best medical treatment will be offered to the whole group. Smoking advice will be given and hypertension will be carefully controlled and monitored. The patients will be asked if they will be prepared to have an EVAR device in the future and if so to have CT scan or angiogram to see if their aorta would be potentially suitable for correction by an endovascular device should this be required. Patients will then be randomised to receive EVAR or not. The risks of EVAR and the potential for needing to correct by urgent open repair would be described. Undoubtedly some patients would not wish to undergo randomisation and this patient preference would be respected. Others will press for EVAR and trialists believe we should see if we can recruit patients prepared to be randomised. If trialists explain to patients that EVAR *could* be beneficial but that there is no certainty, equipoise could be achieved with some difficulty. The alternative is that some surgeons will just put them in and other centres will put in no EVAR devices. The role of a monitoring committee would be vital here as it must be possible to say to a patient that outcomes are being monitored and if EVAR looks beneficial it will be offered to that patient later. It is considered that patient preference should not formally be sought but if during the discussion before randomisation, a strong patient preference emerges this will, of course, be recognised and randomisation only applied to the equipoise patients, but no NHS funding is available for EVAR devices except as part of the randomised controlled trials, EVAR 1 & 2.

Figure 4 demonstrates the entry protocol for patients into both trials.

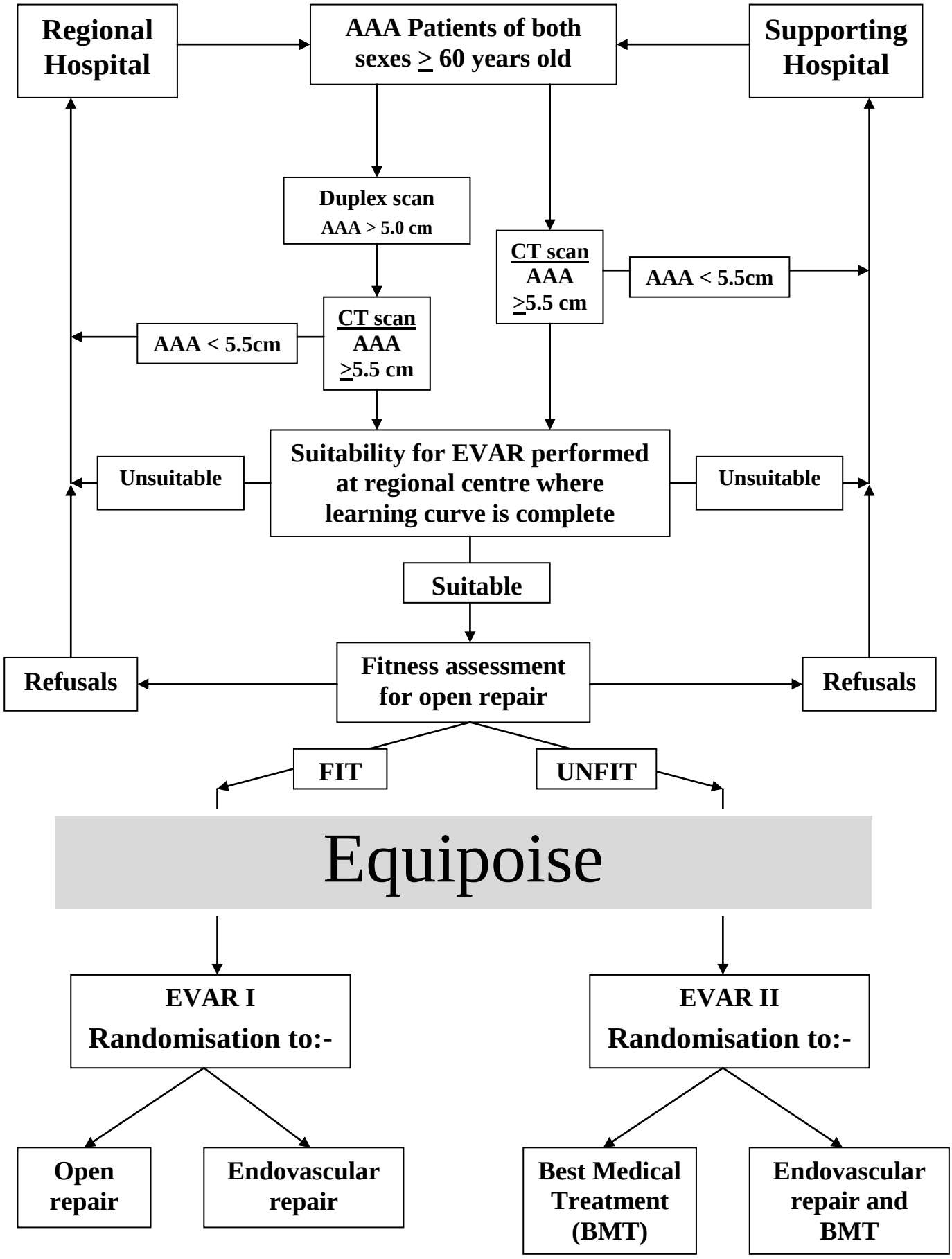


Figure 4 – Summary of recruitment procedure for EVAR Trials

3.6 Triggering of treatment costs on randomisation to an EVAR device

The use of stents over open repair carries a significant increase in treatment costs. Following negotiations with The NHS Executive (North Thames London Region) it was agreed that treatment costs may be reimbursed to each trial centre on randomisation for an EVAR device. Service costs are unlikely to be funded. An assessment of costs was carried out to ascertain the excess treatment cost expenditure associated with an EVAR repair over an open repair (OR) or best medical treatment. According to Höltzenbein *et al*[14] 80% of costs associated with AAA repair can be accounted for by, 1) total length of stay, 2) days in ITU, days in HDU, 3) theatre costs. Estimates were made and are given in Figures 5 and 6. Thus, a patient randomised for EVAR in EVAR Trial 1 will require £6,465 additional funding triggered to the relevant NHS provider Trust on a named patient, named operator and named centre basis. Similarly, a patient randomised to EVAR in EVAR Trial 2 will require £9,139 of triggered funding.

3.7 Financial provision for complete data collection

It is essential that high quality data is collected for all patients randomised in the EVAR Trials. To encourage good data retrieval, trial co-ordinators based at each of the 13 participating centres will be paid an additional amount of money on receipt of clean and complete data at Charing Cross. An estimate has been made of the length of time a trial co-ordinator will take to complete the case report forms, (1 hour for a baseline assessment and 20 minutes for a follow up appointment). A £25 payment will be made for each complete baseline assessment and a further £25 payment for the operation data. A £25 payment will also be made on receipt of each complete set of follow-up data.

Treatment costs	**EVAR**	**OR**
Theatre, surgeon, anaesthetist, nurse, sutures, current device *	3.7 hours = £924	3.7 hours = £924
AAA repair device **	£5,000	0
Wires, catheters for radiologists **	£800	0
Consultant radiologist *** (2 day)	£378	0
Senior radiographer grade I *** (2 day)	£146	0
Radiology nurse, Grade F *** (2 day)	£141	0
Post operative CT scans (£250 each) at 1/12, 3/12, 6/12, 1, 2, 3, 4 years	£1,750	£1,750
Totals	**£9,139**	**£2,674**

Net treatment cost for EVAR 2 = £9,139
(70 randomised per year => 35 for EVAR)

Net treatment cost for EVAR 1 = EVAR - OR
= 9,139 - 2,674 = £6,465
(200 randomised per year => 100 for EVAR)

* taken from "Resource use and costs of elective surgery for asymptomatic abdominal aortic aneurysm" *R.G. Jepson, J.F. Forbes, F.G.R. Fowkes* European Journal of Vascular and Endovascular Surgery, 1997, Vol 14.

** Manufacturers price lists

*** NHS salary scales 1998

Figure 5 -Treatment costs of EVAR (EVAR Trial 2) and net costs over OR (EVAR Trial 1)

Service costs	**EVAR**	**OR**
Pre operative duplex and CT scans *	£513	£513
Pre operative assessment days ** (standard rate, £112 per day) *	2 days = £224	1 day = £112
Post operative ITU days ** (standard rate, £797 per day) *	0	1 day = £797
Post operative HDU days ** (standard rate, £398 per day) *	7 days = £2,786	0
Post operative standard days ** (standard rate, £112 per day) *	0	9 days = £1,008
Totals	**£3,523**	**£2,430**

Net service cost for EVAR 2 = £3,523

Net service cost for EVAR 1 = EVAR - OR
= 3,523 - 2,430 = £1,093

* taken from "Resource use and costs of elective surgery for asymptomatic abdominal aortic aneurysm" *R.G. Jepson, J.F. Forbes, F.G.R. Fowkes* European Journal of Vascular and Endovascular Surgery, 1997, Vol 14.

** taken from "UK Small Aneurysm Trial" papers Lancet 21st November 1998

Figure 6 – Outline of service costs for EVAR and Open Repair (OR)

4. Outcome measures

4.1 Mortality

EVAR Trial 1

From The UK Small Aneurysm Trial data, 30 day operative mortality was calculated for patients who were randomised to observation but whose aortic aneurysms subsequently grew to > 5.5cm when surgery was performed (n=191). 11 were dead at 30 days leading to a 30 day operative mortality of 5.76%. For sample size calculations we have used this figure as 30 day operative mortality for AAA $\geq$ 5.5cm by open repair (OR).

During the three years that RETA has been auditing the UK EVAR experience the 30 day mortality has improved steadily (see Figure 2). This has led to the possibility that EVAR Trial 1 will provide an answer in terms of operative mortality differences between open repair and EVAR. Figure 7 shows how the numbers required for this Trial have reduced such that we may need to randomise as few as 361 patients in each arm (722 in total). Sample size calculations were calculated to provide 90% power at the 5% significance level.

EVAR Trial 2

From the UK Small Aneurysm data, we know that unfit for OR patients with best medical treatment have a mortality at 10 months of 22% and 50% at 2 years. The Nottingham 30d EVAR mortality at 10 months for patients unsuitable for OR is 40%. We could expect to recruit at least 70 patients per year unsuitable for OR but suitable for EVAR and so approximately 300 in 4 years.

We are extremely grateful to Dr Astrid Fletcher for suggestions, particularly with respect to building in stopping rules, during trial monitoring. She suggested we take the control group mortality as 25% per annum and assume the expected between group relative difference of around 45% (absolute difference of around 20%) using a 2 tail test to allow for both a possible benefit or possible adverse effect of EVAR. At 90% power and 1% alpha we need around 734 patient years. Alpha is increased to take account informally of 3 looks which would overall give a lower alpha. This can be achieved by randomising 300 patients over 4 years and assuming an average follow-up per patient of 2.5 years with a further minimum one year follow-up to achieve the required number of patient years. If we randomise more patients earlier then we will accrue more patient years more quickly. Then assuming an overall death rate of 30% in the 2 groups if EVAR is worse by 20% or if EVAR is better we will have between 150 to 225 deaths. We could then plan 3 looks based on 75 deaths with stopping rules built in. However if the mortality is lower because EVAR is better we will not get this number of deaths. It would be "safer" to recruit more patients from the outset. If we could recruit 440 patients over the 4 years then we could accumulate 1,000 patient

Sample size calculations are calculated to provide 90% power at the 5% significance level.

	Open repair [UK Aneurysm Trial]	EVAR [Original grant application]	EVAR [RETA 1996 data]	EVAR [RETA 1997 data]	EVAR [RETA 1998 data]
Number dead at 30days / Total operated	11 / 191	6 / 91	8 / 96	4 / 126	2 / 180
30 day operative mortality	5.76 %	6.6 %	8.3 %	3.2 %	1.1 %
Numbers required per group (total recruitment) to detect difference between EVAR and OR		17,504 (35,008)	2,205 (4,410)	1,448 (1,896)	361 (722)

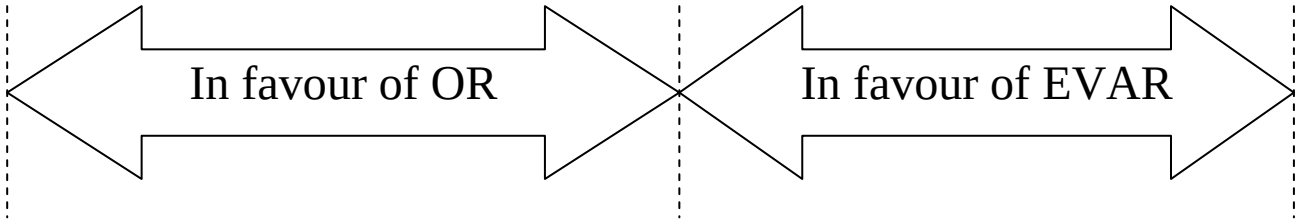


Figure 7 – Numbers of patients required for EVAR Trial 1 to detect a difference in 30 day operative mortality between Open Repair (OR) at 5.76% and EVAR mortality figures according to year of RETA audit.

years (especially with fast and early patient recruitment) then 3 looks could be carried out every 100 deaths. This would also preserve a higher alpha value over the looks. So we would not need to wait 4 years to start the first analyses, it would depend entirely on the accrual of death and patient years. We should get the first 300 or so patient years by year 3. The monitoring committee would check (1) patient recruitment (2) deaths and advise the Steering Committee of any adjustments for recruitment etc. as necessary.

4.2 The incidence of endoleaks from EVAR (Safety of Procedure)

A CT scan is performed on all EVAR patients in the first month after operation seeking endoleak. Endoleak is extremely important to find particularly at the top end where blood flow between the stent graft system and the aortic wall can increase pressure on the aortic wall, greater than if the stent graft system was not in place. If uncorrected, mortality follows. Endoleak is checked at the time of the procedure with contrast radiography but if the upper end works loose, endoleak from there could occur and is best detected (at this state of knowledge) by CT scan with contrast. Additional procedures to correct endoleak such as the use of additional stents with covered grafts will be carefully noted. This is an important outcome measure and critical to assure safety and efficacy of the procedure. It will also affect costs and patient anxiety. Endoleak is conveniently classified in the manner suggested by Geoffrey White of Sydney, Australia [15]:

Endoleak type I	Perigraft leak at proximal or distal end
Endoleak type II	Retrograde endoleak from patent lumber artery, inferior mesenteric artery, intercostal artery or other (renal, internal iliac, subclavian etc.)
Endoleak type III	Fabric tear
Endoleak type IV	Graft porosity
Endoleak type V	Endopressure

4.3 Health Related Quality of Life (HRQL)

In measuring HRQL a combination of specific and generic instruments is recommended e.g. [16]. Specific instruments are useful for clinical evaluation; their narrow focus makes them more responsive to small but clinically important changes in health. Generic instruments are useful for economic evaluation and for comparisons across groups of patients; their comprehensive nature also enables them to detect unforeseen effects of treatment. There are two main types of generic instrument - health profiles and utility measures. Health profiles measure HRQL across a number of distinct dimensions and thus assess the effect of health care on different aspects of HRQL. Utility measures incorporate the values that individuals

attach to HRQL and thus produce a single index of HRQL suitable for economic evaluation.

The portfolio of instruments to measure HRQL in the proposed trials is designed to be comprehensive yet brief. It will be completed by patients in the form of a questionnaire - at recruitment and subsequently one, three and 12 months after surgery or the beginning of medical treatment as appropriate. The questionnaire will include two generic instruments - the Short-Form 36-item (SF-36) Health Survey and the EuroQol. The SF-36 is a health profile comprising eight distinct scales including physical and social functioning, role limitation, mental health, vitality, pain and general health[17]. It has been shown to be valid, reliable and responsive to changes in health in British patients [18-20]. The EuroQol is a validated utility measure comprising five items covering mobility, self care, usual activities, pain, anxiety and depression[21]. The HRQL states defined by the various combinations of responses to these items have been valued by the general public for use in cost-utility analysis. Unfortunately we know of no specific instrument designed to measure HRQL in patients suffering from AAA; this has been confirmed by a recent systematic search of Medline. One likely reason for this lack is the wide range of effects that this condition has on patients. In these circumstances we propose to use the State Trait Anxiety Inventory (STAI)[22] which encompasses both the state form (transitory feelings of fear or worry) and the trait form (the stable tendency to respond anxiously to stressful situations or proneness). The STAI measures in-built tendency to anxious response and current feelings of anxiety. It enables the investigator to distinguish between the transitory (state) and the dispositional types of anxiety.

We also propose to use The Patient Generated Index (PGI). This is a quasi-specific HRQL instrument that focuses on the concerns of the *individual* patient with a given condition rather than concerns derived by the investigator for the *typical* patient with that condition[23]. Patients nominate and rate on a scale the five most important aspects of their lives affected by their health. The final score represents the gap between their current health status and their expectations in those areas of their lives in which they would most value an improvement. Thus the PGI measures the effect of the condition on quality of life as defined by the patient. There is good evidence for the acceptability, validity, reliability and responsiveness of this instrument.

4.4 Economic Evaluation

Within each of the two sub-trials the type and extent of economic evaluation will depend crucially upon the clinical outcome of that trial:

1. If one technology produces a clinically better outcome than another at significantly lower cost, then clinical and financial criteria both lead to the same conclusion.
2. If there is no clinically significant difference in outcome between two technologies under comparison, then the least cost option is preferable (cost minimisation analysis[24]).
3. If one technology produces a clinically better outcome than another at higher cost, then we shall undertake marginal cost-utility analysis[24] (based on mortality and the EuroQol[21]) and, if appropriate, marginal cost-effectiveness analysis[24] (based on the Patient Generated Index (PGI)[23]).

NHS costs will be collected. These will include the length of time in hospital (subdivided into intensive care, high dependency care, acute care and convalescent care), and theatre costs (subdivided into the length of operation and the use of staff, tests and drugs).

Under scenario 3 we shall use the EuroQol to estimate changes in health utility. One advantage of using the EuroQol is that it expresses changes in HRQL on a ratio scale. Thus cost-utility ratios in the form of cost per quality-adjusted life year (QALY) can be constructed from changes in mortality (if any) and in HRQL. Comparisons can then be made with other health care interventions. If there is no significant change in mortality, however, care will be needed because the EuroQol is less responsive to change than most condition-specific measures. To reduce the possibility of a Type II error, we shall also undertake a cost-effectiveness analysis based on the PGI.

We shall subject our results to extensive sensitivity analysis. First we shall identify the critical components of the cost and outcome by varying all estimated parameters in the analysis individually, to see how the economic findings are affected. Those parameters which lead to substantial changes in these findings will be varied over plausible ranges in combination to see whether the main conclusions are altered[25].

As this economic evaluation is being undertaken alongside a randomised trial, both cost and outcome data will be subject to random variation. Therefore we shall estimate confidence intervals for costs, outcomes, cost-utility ratios and cost-effectiveness ratios. The last two will use the resampling technique known as bootstrapping [26].

4.5 Follow-up

All trial patients will be ONS flagged for mortality. HRQL data will be collected at 1, 3 and 12 months following treatment for those allocated to an operation. However, for patients randomised to best medical treatment in EVAR Trial 2 we have incorporated a 1 month delay for the early follow-up in these patients. This takes into account the estimated 1 month delay patients will experience waiting for their EVAR procedure in the EVAR arm of trial 2.

Cost evaluation will be based on operation costs and in patient admissions during the course of follow up. The incidence of any adverse events will also be collected at every follow-up appointment, eg. tender AAA, ruptured AAA, conversion to open repair, myocardial infarction, stroke, renal failure and amputation. CT scan will be used for assessment of growth rates, persistent endoleaks and durability which could vary with stent graft type. CT scan follow-up will be at 1 and 3 months, 1 year, 2 years, 3 years and 4 years for EVAR patients in trial 1 or 2. CT scan follow up will be performed annually for patients randomised to EVAR Trial 1 OR. CT scan follow up will be annually for best medical treatment patients in EVAR Trial 2. Creatinine will be recorded annually for all patients to assess any changes in renal function between the randomised groups.

Figure 8 illustrates the treatment procedure for each patient.

Patient has met eligibility criteria :-

- **≥ 60 years of age**
- **Maximum AAA diameter ≥ 5.5cm according to CT scan**
- **AAA anatomically suitable for endovascular repair**
- **Fitness status and suitability for EVAR 1 or 2 established**

↓

Baseline assessment including Health Related Quality of Life (HRQL) questionnaire completed at regional centre and received at EVAR trial co-ordinating centre. Patient has given informed consent by signing consent form

↓

Randomisation performed centrally by Louise Brown + **Patient flagged for mortality at Office of National Statistics (ONS)**

↓

Treatment carried out at regional centre

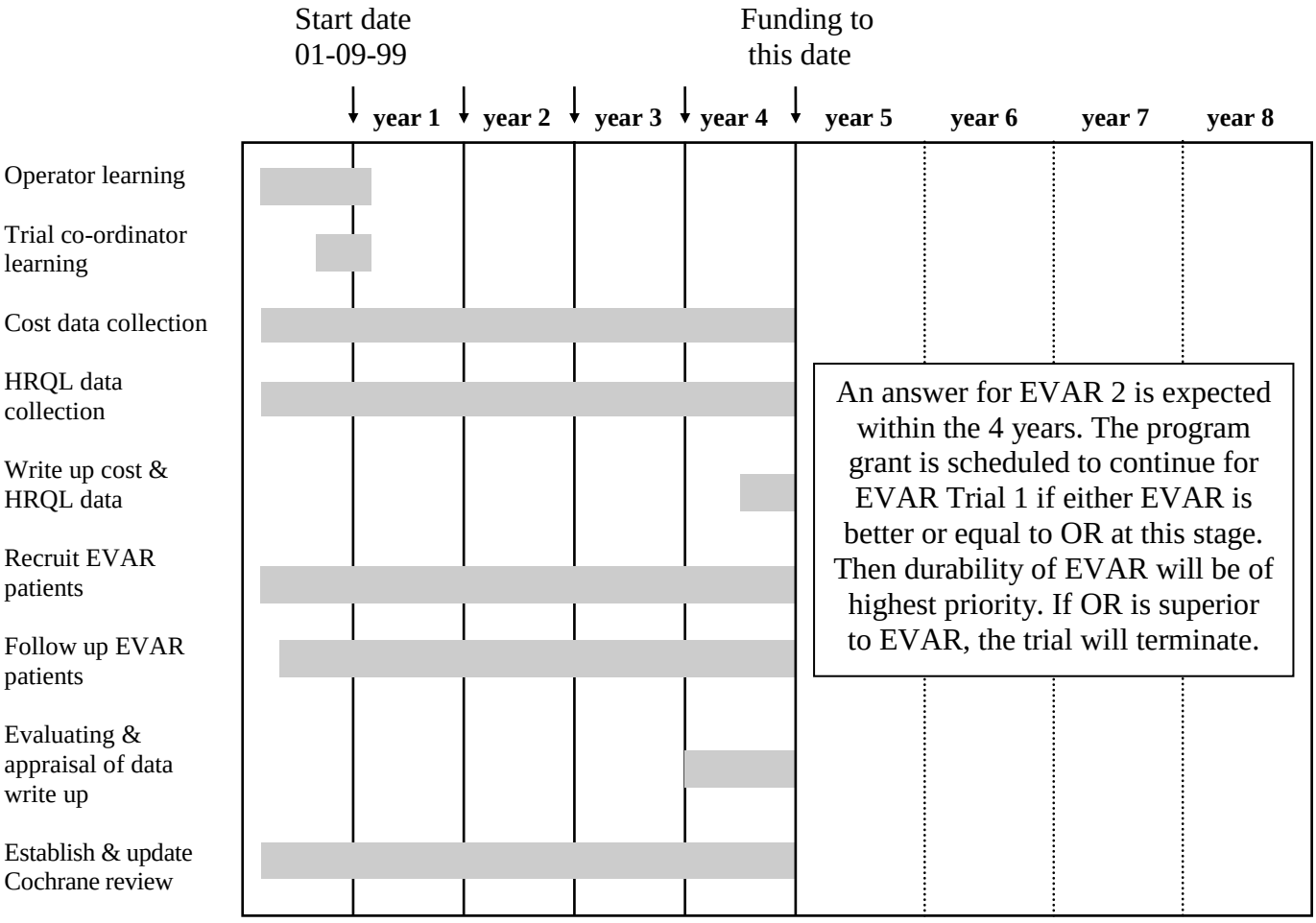
↓

Data to be collected at each follow up appointment

	EVAR Trial 1		**EVAR Trial 2**	
Follow up interval	**EVAR** Follow-up from operation	**Open repair** Follow-up from operation	**EVAR + best medical treatment** Follow-up from operation	**Best medical treatment** Follow-up from randomisation
1 month	CT scan HRQL	HRQL	CT scan HRQL	None
2 months	None	None	None	HRQL
3 months	CT scan HRQL	HRQL	CT scan HRQL	None
4 months	None	None	None	HRQL
1 year	CT scan HRQL Creatinine	CT scan HRQL Creatinine	CT scan HRQL Creatinine	CT scan HRQL Creatinine
2 years	CT scan Creatinine	CT scan Creatinine	CT scan Creatinine	CT scan Creatinine
3 years	CT scan Creatinine	CT scan Creatinine	CT scan Creatinine	CT scan Creatinine
4 years	CT scan Creatinine	CT scan Creatinine	CT scan Creatinine	CT scan Creatinine

Figure 8 – Patient treatment procedure within EVAR Trials

5. Project Milestones of the program grant



Operator learning curves are completed for 13 centres. The RETA registry has recommended that these centres should form the initial regional trial participants. The 13 co-ordinators have been trained at Charing Cross trial centre in London. Patients will be recruited to both EVAR trials for the whole of the four year period. Follow-up commences from discharge of the first patients and exceed three years for the early patients entered. Evaluation and appraisal of data will be undertaken during the fourth year during which there would need to be close liaison with the DMEC. This committee would play a vital role in both trials. In Trial 1 the monitoring committee will determine and track mortality in OR v EVAR and be in a position to predict if a result is likely and if so when. During the period of this investigation safety, efficacy and durability of EVAR in that trial will be established. If there is any possible chance of showing a difference in mortality in favour of EVAR, EVAR would potentially be the most cost effective method of treating AAA within the NHS. Much shorter hospital stays and reduced pain from absence of the large abdominal incision would be clear advantages.

In Trial 2 the monitoring committee review the mortality closely in the two arms and apply stopping rules if EVAR is clearly showing no adjuvant benefit beyond best medical treatment. If EVAR was abandoned for unfit for OR patients this would constitute great savings to the NHS. If the trial is not performed, we believe that there will be operator pressure for the NHS to provide EVAR in these patients, as these are the type of patients first treated successfully by EVAR. The NHS has funded EVAR Trials 1 and 2 with the intention that NHS money for EVAR procedures will only be available within these trials until an answer is known.

6. Methods for Disseminating and Implementing Research Results

Results will be presented to the Cochrane Research Group for Vascular Disease in Edinburgh and the NHS Centre for Review and Dissemination in York. We would certainly follow the guidelines of the Research and Development Directorate for reporting research results in the NHS**.** Results would be presented to National and International peer reviewed journals and offered for presentation at national and international societies. In this regard the applicants are well placed within key societies and various discipline groups in the UK and Europe.

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