WORKING GROUP ON ACUTE PURCHASING

The Use of Endovascular Stents for Abdominal Aortic Aneurysm

December 1999

GUIDANCE NOTE FOR PURCHASERS 99/08

Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 12 October 1999 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF ENDOVASCULAR STENTS FOR ABDOMINAL AORTIC ANEURYSM

AUTHORS: Calvert NW, Lloyd Jones M, Thomas SM, Richards RG, Payne JN. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1999. Guidance Note for Purchasers: 99/08.

EXPERT ADVISORS TO TRENT DEC:

Dr R G Richards, Consultant in Public Health Medicine, North Nottinghamshire Health Authority.
Dr S M Thomas, Endovascular Research Fellow, Northern General Hospital, Sheffield.

(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The Committee recommended that endovascular abdominal aortic aneurysm repair should only be purchased in the context of national clinical trials.

December 1999

THE USE OF ENDOVASCULAR STENTS FOR ABDOMINAL AORTIC ANEURYSM

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Dr M E Dewey (Acting) (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority And Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst
Chairman, Trent Working Group on Acute Purchasing

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EXECUTIVE SUMMARY

Description of the proposed service: Endoluminal repair of abdominal aortic aneurysm (AAA) instead of open surgical repair.

Epidemiology: Prevalence of aneurysms >49mm in diameter is estimated at around 120 per 100,000 in the age group 50-79. AAAs are more common in males and prevalence increases at older ages.

Number and quality of studies and direction of evidence: No randomised controlled trials, but eight non-randomised controlled studies were found. A total of 481 patients had endoluminal repair and 472 ('controls') had open repair in these studies. Four studies suggested that endoluminal repair had a lower rate of systemic/remote complications than open repair, but in three of these there was a higher rate of local/vascular complications. Peri-operative mortality was similar, although mostly lower with endoluminal repair. The overall success rate of endoluminal repair was between 70-80% (i.e. successful placement, no endoleak and without mortality by 30 days). Long-term outcome studies were not available.

A UK Endovascular Aneurysm Repair (EVAR)1 randomised controlled trial will compare endovascular with open repair in patients suitable for either procedure. The results from the UK small aneurysm trial did not support a policy of open repair for AAAs of 40-55mm in diameter – whether this policy should alter, if endoluminal repair replaced open repair, is not clear from the published evidence. A second Endovascular Aneurysm Repair (EVAR2) trial will compare endovascular repair with a 'watch and wait' policy for patients unfit for open repair.

Costs: Estimates of costs for endoluminal repair vary from 14% less, to 20% more, than for open repair. Costs are very sensitive to Intensive Therapy Unit (ITU) utilisation. Cost estimates using information from one hospital in Trent (Northern General Hospital, Sheffield) suggest costs of treating fit patients of £7,500 for endoluminal repair and £6,300 for open repair. The costs of an endoluminal repair for unfit patients are higher due to a longer hospital stay and are estimated at £8,300. Emergency open repair of ruptured AAA has been estimated to cost up to £13,000.

Cost-effectiveness and cost-utility: No papers were found reporting formal cost-effectiveness or cost-utility. The lack of published evidence on long-term outcome prevents the calculation of life years gained or cost per life year gained. A decision analysis modelling approach could be used to generate initial estimates of cost-effectiveness and to identify threshold values for key variables. Some work in this area is in progress in Sheffield. During the final drafting of this report, early results from the Sheffield work analysing the unfit and the unsuitable for open repair patient groups, indicate that endoluminal repair is likely to be cost-effective for both groups. The EVAR trials in the UK may help to validate the current modelling work.

ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
ACOST	Advisory Committee on Science and Technology
CT	Computed Tomography
ER	Endoluminal Repair
EVAR	Endovascular Aneurysm Repair
HDU	High Dependency Unit
ITU	Intensive Therapy Unit
ODA	Operating Department Assistant
QALY	Quality Adjusted Life Year
RETA	Registry for Endovascular Treatment of Aneurysms
SERNIP	Safety and Efficacy Register of New Interventional Procedures (of the Academy of Medical Royal Colleges)
UKSAT	UK Small Aneurysm Trial

1. INTRODUCTORY REMARKS

Abdominal aortic aneurysms (AAA)s are swellings of the wall of the main descending artery in the abdomen. Untreated, these aneurysms are likely eventually to leak or rupture; an event which, even if surgically treated, carries a high mortality. At present, AAAs are repaired by open abdominal surgery. The new procedure discussed in this report uses a synthetic graft introduced through an artery; it is a less invasive procedure, similar to other 'keyhole' surgery in its implications. This report assesses the evidence for the effectiveness of this new procedure and its impact on costs, including possible changes in treatment thresholds.

2. DESCRIPTION OF UNDERLYING DISEASE

2.1 Epidemiology (incidence and/or prevalence in an average health authority of 500,000 population[a])

Recent population screening surveys, using ultrasonic examination of the aorta, have provided the best estimates of the prevalence of AAAs. The surveys are not all exactly comparable either in terms of the definitions used (i.e. the diameter of the aorta) or the age bands. However, there is general agreement. As with other vascular degenerative diseases, AAAs are more common in men than women and the number increases with age.

The prevalence of small AAAs in elderly men in England depends upon the age group screened and the criteria used for the definition of AAA. 1.3% of the male population aged 50 and over appears to have an AAA when this is defined as an aorta of 46mm or wider, and as many as 5.2% have an AAA using a definition of an aorta wider than 29mm.[1] AAAs are less common in women than in men; the Chichester screening survey found that only 1.3% of women aged between 65 and 80 had an aorta wider than 29mm, compared with 7.6% of men in the same age group (see Table 1).

[a] Age structure as per England and Wales

Table 1 Prevalence of Abdominal Aortic Aneurysms in the General Population found by Screening Surveys in the UK

Location	Authors	Aortic diameter	Sex	Age (years)	Number of Patients Screened	Prevalence
Oxford	Collin et al. 1988[2]	5mm greater than the diameter of the suprarenal aorta	MALE	65-74	426	5.4%
Northumberland	Holdsworth 1994[3]	>49mm	MALE	65-79	628	1.6%
Huntingdon	Morris et al. 1994[1]	≥ 46mm	MALE	≥ 50	3,030	1.3%
Oxford	Collin et al. 1988[2]	>40mm	MALE	65-74	426	2.3%
Oxford	Collin et al. 1990[4]	≥40mm	MALE	65-74	746	2.0%
Gloucestershire	Lucarotti et al. 1993[5]	>40mm	MALE	65	4,232	1.3%
Birmingham	Smith et al. 1993[6]	>40mm	MALE	65-75	2,669	3.0%
Liverpool	Loh et al. 1989[7]	>30mm	MALE	> 55	657	2.9%
Huntingdon	Morris et al. 1994[1]	≥ 30mm	MALE	≥ 50	3,030	5.2%
Birmingham	Smith et al. 1993[6]	>29mm	MALE	65-75	2,669	8.4%
Chichester	Scott et al. 1995[8]	>29mm	MALE	65-80	2,342	7.6%
			FEMALE	65-80	3,052	1.3%
Northumberland	Holdsworth 1994[3]	>29mm	MALE	65-79	628	6.7%
Huntingdon	Wilmink et al. 1998[9]	>29mm	MALE	≥ 50	7,493	5.2%
Gloucestershire	Lucarotti et al. 1993[5]	>25mm	MALE	65	4,232	8.4%
Oxford	Collin et al. 1990[4]	≥25mm	MALE	65-74	746	6.3%
Chichester	Khoo et al. 1994[10]	Unspecified	MALE	65-80	6,078	6.8%
			FEMALE	65-80	5,588	1.2%

Two studies suggest that around 5% of elderly men have an aortic diameter of 25-39mm.[4,5] Whilst an aorta below 30mm in diameter would not strictly be defined as an aneurysm, it has been suggested that, because the behaviour of aortas with diameters between 26 and 40mm is unpredictable, patients with an aortic diameter greater than 25mm should be followed up with annual ultrasonographic scans and referred for surgical assessment should the diameter reach 40mm.[11]

The prevalence of AAA increases steeply with age. Table 2 presents data from those surveys which divided their subjects into age bands. One survey found that, whilst only 0.3% of men aged between 50 and 64 appeared to have an aorta of 46mm or wider, this figure rose to 4.1% of men aged 80 and over, an almost fourteen-fold increase. 2.3% of men aged between 50 and 64 appeared to have an aorta of 30mm or wider, compared with 11.9% of men aged 80 years and over.[1]

Although the prevalence of AAA is substantially lower in women than in men, in women too the prevalence increases markedly with age. One study found that 1.7% of women aged between 71 and 80 had an aorta wider than 29mm, compared with 0.8% of those aged 65 and 70,[8] whilst another found that the prevalence rose from a rate of 0.6% in women aged between 65 and 67 to peak at 2.4% in women aged between 74 and 76.[10]

The prevalence of screen-detected AAA in the UK is very similar to that in other countries in the Western world.[9]

The UK Small Aneurysm Trial (UKSAT)[12] has now indicated that there is no overall benefit in performing open repairs in aneurysms of 55mm and under. The nearest prevalence data to such a figure is from the Northumberland survey,[3] which reported AAAs greater than 49mm in 65-79 year old men at a prevalence of 1.6%. A male/female ratio of about 6:1 in this age group was recorded in other studies[8,10] and, although this was not specifically at the size of greater than 49mm, this gives the best available estimate of the prevalence of these larger AAAs in women. The Huntingdon survey[1] gives a ratio for 50-64 years of age to 65-79 years of 1:8 in men for AAAs greater than, or equal to, 46mm, which would imply a rate of AAAs greater than 49mm amongst 50-64 year olds of less than 0.2% for men and 0.03% for women. Thus, Table 3 gives an indication of prevalence of aneurysms of greater

than 49mm for an average English health authority and primary care group populations.

Table 2 Prevalence of Abdominal Aortic Aneurysms in the General Population found by Screening Surveys in the UK, by Age

Location	Authors	Aortic Diameter	Sex	Age (years)	Number of Patients	Prevalence
Huntingdon	Morris et al. 1994[1]	≥ 46mm	Male	50-64	1,776	0.3%
				65-79	1,061	2.5%
				≥ 80	193	4.1%
Liverpool	Loh et al. 1989[7]	>30mm	Male	55-64	Not stated	1.3%
				> 65	Not stated	6.5%
Huntingdon	Morris et al. 1994[1]	≥ 30mm	Male	50-64	1,776	2.3%
				65-79	1,061	8.8%
				≥ 80	193	11.9%
Chichester	Scott et al. 1995[8]	>29mm	Male	65-70	1,091	5.9%
				71-80	1,251	9.1%
			Female	65-70	1,341	0.8%
				71-80	1,711	1.7%
Chichester	Khoo et al. 1994[10]	unspecified	Male	65-67	2,830	5.4%
				68-70	1,520	7.0%
				71-73	602	9.6%
				74-76	560	8.6%
				77-79	471	10.4%
				80	95	1.1%
			Female	65-67	2,438	0.6%
				68-70	930	1.3%
				71-73	711	1.3%
				74-76	718	2.4%
				77-79	632	2.1%
				80	159	0.6%

Table 3 Estimated Prevalence of Abdominal Aortic Aneurysms >49mm in Populations of 100,000 and 500,000

Age (years)	% Male	% Female	Males/ 100,000 population	Females/ 100,000 population	Total for 100,000 population	Total for 500,000 population
50-64	0.2	0.03	16	3	18	91
65-79	1.6	0.27	83	18	101	504
50-79			99	20	119	595

On the basis of re-screening 682 men with normal initial scans, one study has calculated that, between the ages of 65 and 70, new cases develop at a rate of 3.7% over five years.[10] Whilst this represents an annual incidence of 0.75% for this age group, it is difficult to use this figure to estimate for the entire population, especially as this paper did not indicate the threshold size of aneurysm. Current activity in Trent suggests that rates of admission for AAA are 7.7 per 100,000 and 7.3 per 100,000 per annum for elective and emergency admissions respectively.[13] In a 'typical' district of 500,000 residents, therefore, 38 elective and 36 emergency AAA admissions respectively can be expected per annum.

2.2 Pathology and Prognosis

Aortic aneurysm has also been defined as a focal dilatation of the aorta involving an increase in diameter of at least 50% compared with the expected normal diameter[14] or, in the case of AAA, a luminal diameter greater than 30mm.[15] 89% of all abdominal aneurysms affect the infrarenal aorta.[15]

The best predictor of AAA development is a positive family history of the condition.[16] As has been seen, advancing age is also an important factor. Population-based screening surveys show that male sex and smoking are also important risk factors (relative risk 6.5 and 2.9 respectively). These surveys also indicate that patients with peripheral vascular disease and cardiovascular disease are twice as likely to have an AAA as those without those diseases. Hypertension is associated with a mildly increased risk of AAA (relative risk 1.5), but diabetes and hypercholesterolaemia are not associated with an increased risk.[9]

For technical and ethical reasons, the natural history of AAAs has not been precisely determined.[16] However, it is clear that untreated aneurysms are likely to expand and, eventually, rupture, although the rates of expansion and frequency of rupture

are unpredictable. 25 to 41% of aneurysms larger than 50mm in diameter rupture within five years, and aneurysms of 40-50mm in diameter, have been reported to have five-year rupture rates of 3 to 12%, although data relating to these smaller aneurysms are sparse.[14]

Up to 62% of patients with ruptured aneurysms die before reaching hospital.[17] When these pre-hospital deaths are combined with the mortality rate of approximately 50% associated with repair of ruptured AAAs, the overall mortality rate after rupture may exceed 80%.[14] Moreover, the quality of life declines after emergency repair for rupture.[18] The urgent repair of symptomatic, unruptured AAAs is also associated with increased mortality and high morbidity in comparison with elective aneurysm repair.[19]

Most deaths due to rupture are potentially preventable by elective repair of the AAA. However, it is not clear at what point that repair should, ideally, be undertaken. It has been argued on the one hand that elective surgery is inappropriate for aneurysms under 50mm in diameter because the rupture rate is negligible and would be outweighed by the risks associated with the intervention.[20] This view is supported in respect of open repair by the UKSAT results.[12] On the other hand, some argue that early surgery would generally improve survival in patients with AAAs less than 50mm in diameter, although watchful waiting is generally preferable for those with AAAs less than 40mm in diameter.[21] The debate will not be resolved fully until the results are available from the three ongoing multicentre trials which seek to identify appropriate criteria for the elective repair of small AAAs.[22] However, it is clear that, because of the dramatic increase in rupture risk for AAAs larger than 50-60mm, nearly all patients with an AAA of this size benefit from elective repair, unless the operative risk is very high.[21]

2.3 Significance in Terms of Ill-Health (Burden of Disease)

2.3.1 Asymptomatic AAA

80% of AAAs are asymptomatic and are only detected either by imaging studies done for other reasons,[16] or after death.[2] Therefore, accurate information on the incidence of asymptomatic AAA is difficult to obtain. Reported incidences vary between 3.0 and 117.2 per 100,000 per annum.[9]

All studies report sharp rises (from 4.2 to 11% per year) in the age-adjusted incidence of AAA in recent years. However, as incidence rates have generally been

estimated on the basis of the number of hospital admissions for elective repair of asymptomatic aneurysms, this apparent rise may be due, at least in part, to increased case finding resulting from the increased use of ultrasonography.[9]

2.3.2 Ruptured AAA

Ruptured AAA is extremely uncommon before the age of 55.[5] However, although death from ruptured AAA is rare before the age of 50, it becomes increasingly common in men over the age of 55.[2] 1.36% of deaths in men and 0.45% of deaths in women over the age of 65 in England and Wales are due to this cause.[9] Its greatest impact is in men aged 70-74 years, among whom it accounts for 1.8% of all deaths. Ruptured AAA is much less common in women under the age of 80 and, at its peak, accounts for 0.6% of all deaths in women aged 80-84.[2]

The recent reported incidence of ruptured AAA varies from 1 to 21 per 100,000 per annum. The Goteborg study[23] found a sevenfold rise in incidence over a 36-year period, and this was not entirely due to an ageing population as the age-standardised mortality rate of ruptured AAA also rose by 2.4% per year. However, the reported rise in incidence may be due in part to an increased level of reporting caused by an increased awareness of the condition.[9]

3. CURRENT SERVICE PROVISION

There is as yet little evidence of an effective medical treatment for AAA, although randomised controlled trials of propranolol in patients with small aneurysms are underway.[9] Currently, therefore, the only intervention known to prevent ruptured aneurysm is elective repair of asymptomatic lesions over a certain size. Until recently, open repair has been the only alternative to conservative treatment.

3.1 Open Repair

To prevent rupture, surgical treatment has been recommended for all symptomatic AAAs, and for asymptomatic aneurysms larger than 55mm in diameter, provided that such treatment is not precluded by coexisting conditions.[14] It was also suggested that early surgery was preferable to expectant observation for all aneurysms between 40-50mm in diameter, unless they are in patients who are at increased surgical risk and at low risk for acute aneurysm expansion.[21] However, as discussed earlier, the UKSAT[12] has recently reported no advantage in terms of mortality rates in a policy of open elective surgery compared with ultrasonic surveillance for those with aneurysms of 40-55mm in diameter. It was concluded that 'our results do not support a policy of open surgical repair for abdominal aortic aneurysms of 40-55mm in diameter'. Absence of reliable data on aneurysm expansion rates makes it hard to determine whether there are sub-groups of patients with smaller aneurysms which might benefit more from early surgery.[24]

Open surgery for AAA has been carried out since the fifties. Mortality after such surgery usually lies between 2-7%,[19] and post-operative complications, which occur on average 3-5 years after aortic reconstruction, may increase the overall mortality rate by a further 2%.[18] Other disadvantages of open surgery include lengthy hospital stays, post-operative pain and the possibility of sexual dysfunction.[19] However, the quality of life after elective repair is good.[18]

In patients over 75 years of age, peri-operative mortality for open repair exceeds 20%, even for elective procedures. The most important risk factors in these patients are severe cardiac, renal and pulmonary disorders and morbid obesity.[15]

3.2 Conservative Treatment

Conservative treatment may imply one of the following options:

- no treatment (for patients unfit to survive any intervention, or who appear, because of other conditions, such as, malignant disease, to have only a short time for survival following intervention);
- intervention only on an emergency basis (for patients who are unfit for elective surgical treatment, but may be operated on in case of rupture);
- expectant observation of small AAAs ('watchful waiting').[19]

Conservative treatment also requires adequate management of hypertension and other risk factors, such as, elevated lipids, and advice and help in respect of smoking cessation.

3.2.1 Current Service Cost

The current costs of treating AAAs in an average health authority are crudely estimated at £650,000 per annum.

3.2.2 Variation in Services

Examination of data from the Trent Regional Patient Information System proved problematic, with obvious differences in coding policies between units distorting any genuine variations.

4. DESCRIPTION OF NEW INTERVENTION

4.1 Information on the Proposed Service

Endoluminal repair (ER) is a relatively recent procedure, first performed in 1990. It uses minimally invasive techniques to exclude the aneurysm sac from the arterial circulation by placing, within the aortic lumen, a prosthetic graft inserted from a remote site and fixed in position using expandable wire stents or hook systems rather than sutures. Currently two technologies dominate stent design: self-expanding stents and those requiring expansion by a balloon once in place. One type of device, the aorto-uni-iliac device has to be accompanied by an open procedure to 'crossover' a blood supply to the contra-lateral iliac artery; this is a relatively minor open procedure and can be performed under local anaesthetic in suitable cases.

4.2 Identification of Patients and Important Sub-groups

Because it is less invasive than open repair, ER can reduce the length of hospital stay, and it has been suggested that it is particularly of value in elderly patients and those at high risk from open surgery. As a result, its use has been reported in patients over 80 years of age or with a history of cardiac disease, respiratory disease, end stage chronic renal failure, 'hostile abdomen' (that is, an abdomen affected by extensive scarring or adhesions between organs, that makes surgery within the abdominal cavity difficult and hazardous), haematological abnormalities or previous cerebrovascular accident.[25]

4.3 Criteria for Treatment

Because currently available devices demand precise pre-operative imaging, ER is of little value in cases of rupture.[24] Therefore, it has been used largely for elective repair, although it has also been used successfully on leaking aneurysms.[26]

For anatomical reasons, not all AAAs are suitable for ER. Different categories of stent-graft have been developed to accommodate differences in aneurysm location; within these categories, there is some variation in the method of attaching the device within the aortic lumen.[24] For safe attachment, all three grafts generally require at

least 15mm of normal aorta below the renal arteries.[20] In addition, the aorto-aortic tube graft requires a segment of normal aorta below the aneurysm. The aorto-bi-iliac (bifurcated) graft requires two common iliac arteries of sufficient calibre and length to receive the distal stents, while the aorto-uni-iliac graft requires only one adequate common iliac artery.[27] In addition, most reported delivery systems require the aortic neck to have a diameter no greater than 26mm, although some systems may accommodate grafts suitable for use in vessels up to 30mm in diameter. The iliac vessels must be at least 7-9mm in diameter.[24] Other factors which must be taken into consideration when assessing suitability for ER include concomitant vascular disease, iliac kinking or tortuosity, and iliac, renal or visceral occlusive disease.[28,29] Pre-operative assessment/selection is a crucial element of this intervention.

4.4 Personnel Involved

The procedure is performed by an Interventional Radiologist, a Vascular Surgeon, and Anaesthetist, with support of radiographic, Operating Department Assistant (ODA), and nursing staff.

4.5 Setting

The endovascular procedure is carried out in an operating theatre or radiological suite (with immediate access to a theatre when emergency conversion to open procedure is required), or in a dedicated endovascular theatre, usually in the radiology department with radiological equipment and full theatre level facilities. This allows a combined surgical/radiological approach without compromise of either speciality's facilities.

4.6 Equipment Required

There are a variety of stent devices currently in use. There are three basic anatomical types of stent (tube, aorto-uni-iliac and aorto-bi-iliac), and different designs/ manufacturers of each resulting in a total of 12 forms in use in the UK. Of these, nine are commercially available devices. Some are custom-made for each patient, whilst others come in standard 'off the shelf' sizes. Some other devices, (all aorto-uni-iliac in configuration) are the so-called 'home made' devices, which are constructed at the time of procedure from balloon expandable or self expanding

stents and surgical graft material. Information about the use of stents is now collected by the Registry of Endovascular Treatment of Aneurysms – RETA[b]).

High quality imaging equipment is required, and in some units there is increasing use of computer-aided design software to help with interpretation of spiral computed tomography (CT) imaging and sizing of the device to match the individual patient's anatomy.

4.7 Length of Treatment

Average operating times are similar for ER and open repair, whilst in-patient stays (both Intensive Treatment Unit (ITU) and ward) are likely to be shorter once research and/or ethically driven demands for intense monitoring during trials are no longer necessary.

4.8 Follow-up Required

The length of follow-up for ER is currently distorted by the need to monitor an experimental procedure.

4.9 Degree of Diffusion

In 1996, 1997 and 1998, 14, 23 and 26 centres respectively reported to the RETA. There have been a total of 30 centres reporting cases to RETA between 1996 and 1998; four reported no cases in 1998, having done so in previous years, but this does not mean that there was no activity at those centres. University Hospital, Nottingham has reported the largest series of 112 cases, and centres in the Trent region have reported 30% of registered cases in the UK. 15 centres (50%) have each registered more than 10 cases over the three years.

There were three more types of stent recognised by RETA at the end of 1998 (12) compared to 1997 (9).

[b] Third Report on the Registry for Endovascular Treatment of Aneurysms – prepared on behalf of the Joint Working Party of the Vascular Surgical Society of Great Britain and Ireland and the British Society of Interventional Radiologists, 1999.

4.10 Anticipated Disbenefits

Problems associated with ER include post-operative dilatation of the neck of the aneurysm leading to stent migration, endoleaks which may lead to early aneurysmal rupture,[19] macro- or micro-embolic events, renal dysfunction and intestinal infarction.[18] Reported mortality associated with the procedure ranges from 0-13%, depending on the characteristics of the patients involved. In addition, some patients will need urgent conversion to open repair, and this may involve modifications to the standard open technique, which result in a higher than average morbidity and mortality rate.[19]

The high rate of early complications following ER includes complications exclusive to endoluminal surgery:- post-implantation pyrexia; injury to common femoral or iliac arteries; groin wound complications; and renal impairment which may result from the administration of large quantities of intravenous contrast agent. It has been suggested that complications which are common to both endoluminal and conventional repair generally have a similar incidence regardless of method, but that the overall incidence of peripheral embolic events following endoluminal surgery is less than that described for conventional repair.[24]

Most late complications of ER can be attributed to the development of endoleaks, defined as the persistence of blood flow outside the graft lumen, but within the aneurysm sac or adjacent vessels in which the graft is deployed. Endoleakage is a complication exclusive to ER. Late endoleaks can occur as a result of failure of the proximal or distal attachment device to remain in close apposition to the vessel wall or, with modular devices, the disruption of the contra-lateral limb, the so called 'stump dislocation'. This may be due either to inappropriate patient selection, leading to the deployment of endoluminal devices in less than ideal aneurysm morphology, or to malpositioning of the device.[24] Another contributor, particularly to stump dislocation, is changes in the morphology of the aneurysm after treatment. This can result in shortening and kinking of the main body of the device.

Although long-term results are not yet available, it has been suggested that, as the technology improves, ER will offer the potential for lower morbidity and mortality, and cost savings, in comparison with open repair.[19]

4.11 Suitability of Abdominal Aortic Aneurysms for Endoluminal Repair

A number of studies have attempted to assess the proportion of patients who are suitable for ER. The results of the relevant studies, which have been published in English, are set out in Table 4. As may be seen, estimates of suitability range widely between 9% and 66%. The lowest figures come from studies which pre-dated the production of a reliable, commercially available, bifurcated graft and, therefore, only assessed suitability for tube grafts; their authors felt that, were a reliable bifurcated graft available, over 50%[30] to as many as 73%[31] of the patients would have been suitable for ER. Later studies, which also assessed suitability for bifurcated or aorto-uni-iliac grafts, suggest that these estimates were perhaps slightly optimistic.

The authors of one study, which compares the suitability for ER of aneurysms of different size, suggest that, because aneurysms over 70mm in diameter have significantly wider and shorter necks than smaller aneurysms, they are less suitable for ER. Nonetheless, such repair appears to be feasible in 38% of these larger aneurysms.[32]

Although the use of more complex techniques has allowed ER to be used in patients anatomically unsuited to tube or bifurcated grafts, it has been suggested that the stress involved in the lengthy procedures required may be no less than that of standard open surgery.[20]

Not all patients have aneurysms suitable for ER; currently, at least 45% of patients appear to fall into this category. Estimating the proportion of patients with AAAs suitable for ER is problematic, especially since the publication of UKSAT.[12] The survey which comes closest to the >55mm size of UKSAT,[33] has just 110 patients and has the highest proportion suitable of all the surveys. Any future study of the use of ER of small aneurysms would need to enable sub-group analysis by size of aneurysm, so as to establish the treatment threshold; only then can an estimate of subsequent activity be attempted.

RETA indicates that about 20% of cases were unfit, and about 8% fit, but unsuitable for conventional open repair, suggesting that, if selection criteria currently in use were applied to a new service, total aneurysm repair activity might increase significantly.

Table 4 Suitability for Endoluminal Repair

Authors & Publication Date	Number of Patients	Type of Patient Assessed	% Suitable for Tube Graft	% Suitable for Bifurcated Graft	% Suitable for Aorto-uni-iliac Graft	% Suitable for Graft - Type Unspecified	% Suitable for any form of Stent Graft
Andrews et al. 1995[31]	44	Patients admitted for elective AAA repair	9% (n=4)	-	-	-	9% (n=4)
Moore 1995[30]	69	Patients with a diagnosis of AAA	14% (n=10)	-	-	-	14% (n=10)
Collin 1995[20]	-	Patients with clinically significant AAA	10% (n not stated)	15% (n not stated)	-	-	25% (n not stated)
Lepantalo et al. 1997[34]	63	Patients with AAA > 4mm	-	-	-	27% (n=17)	27% (n=17)
Schumacher et al. 1996[28]	194	Patients admitted for elective AAA repair	-	-	-	29% (n=56)	29% (n=56)
Schumacher et al. 1997[29]	242	Patients admitted for elective AAA repair	-	-	-	30% (n=242)	30% (n=242)
Moritz et al. 1996[15]	77	Patients with infrarenal AAA	14% (n=11)	29% (n=22)	-	-	43% (n=33)
Armon et al. 1997[32]	154	Patients with AAA larger than 45mm	4% (n=6)	10% (n=15)	55% (n=85)*	-	55% (n=85)
Armon et al. 1997[35]	44	Patients with AAA 45-54mm in diameter			57% (n=25)		57% (n=25)
Armon et al. 1997[35]	65	Patients with AAA 55-69mm in diameter			66% (n=43)		66% (n=43)
Armon et al. 1997[35]	45	Patients with AAA ≥70mm in diameter			38% (n=17)		38% (n=17)

* This figure includes those patients found to be suitable for a tube or bifurcated graft, as they were also suitable for an aorto-uni-iliac graft.

4.12 Optimum Timing of Endoluminal Repair

Elective aneurysm repair is undertaken to prevent premature death from aortic rupture. As the rupture rate for aneurysms under 50mm in diameter appears to be negligible,[36] and the risk of rupture in patients with symptomless, slowly expanding AAAs less than 60mm in diameter has been estimated at 0.4%, lower than the risk of elective surgery (1-8%), it has been suggested that such patients should not undergo surgical repair, but should undergo regular ultrasound follow-up.[37] Equally, such patients should not undergo elective ER unless the risk of the intervention can be shown to be less than that of conservative treatment.

It has been suggested that, as AAAs enlarge, the segments of non-dilated aorta above and below the aneurysm progressively shorten, the aorta lengthens and becomes more tortuous, and iliac artery tortuosity also increases, making ER more difficult. However, one study has found that aneurysms with diameters between 55-70mm appear no less suitable for ER than those between 45-55mm in diameter, suggesting that there is no anatomical advantage in operating on small aneurysms rather than waiting until they reach a diameter of 60mm.[32] Given that the operative mortality associated with ER, and the durability of the prostheses, is unknown, there would appear to be no strong argument for pre-emptive ER in patients with small aneurysms.[20]

UKSAT concluded that a policy of watchful waiting until the aneurysm diameter was over 55mm, or was increasing in size at a rate of over 10mm a year, was as good as early open repair in terms of survival. Therefore, if ER has a mortality risk similar to open repairs, there is no justification to perform ER until the aneurysm exceeds 55mm, unless ER mortality rates improve.[12]

5. METHODS

5.1 Search Strategy

The following strategies were used for an initial search using Medline and Embase:

Medline (1995 to 1999)

1 Aortic aneurysm, abdominal/ or 'aortic aneurysm abdominal'.mp.
2 aort$.mp. [mp=title, abstract, registry number word, mesh subject heading]
3 aneurys$.mp. [mp=title, abstract, registry number word, mesh subject heading]
4 abdom$.mp. [mp=title, abstract, registry number word, mesh subject heading]
5 2 and 3 and 4
6 1 or 5
7 stent$.mp. [mp=title, abstract, registry number word, mesh subject heading]
8 6 and 7
9 Blood vessel prosthesis/ or 'blood vessel prosthesis'.mp.
10 6 and 9
11 8 or 10

Embase (1997-1999)

#1 AORT*
#2 ANEURYS*
#3 ABDOM*
#4 #1 and #2 and #3
#5 STENT*
#6 BLOOD VESSEL PROSTHES*
#7 #5 or #6
#8 #4 and #7

Current Contents/Clinical Medicine <11/17/97 - 11/09/98>

1 aort$.mp. [mp=abstract, title, author keywords, keywords plus]
2 aneurys$.mp. [mp=abstract, title, author keywords, keywords plus]
3 stent$.mp. [mp=abstract, title, author keywords, keywords plus]
4 abdom$.mp. [mp=abstract, title, author keywords, keywords plus]
5 1 and 2 and 4
6 blood vessel prosthes$.mp. [mp=abstract, title, author keywords, keywords plus]
7 5 and (3 or 6)

5.2 Inclusion and Exclusion Criteria

As these strategies combined to give a yield of 566 references, an attempt was made subsequently to narrow the search by searching Medline using the strategies detailed below to locate relevant trials, reviews and cost information.

Search for trials

1 exp aortic aneurysm, abdominal/ or 'aortic aneurysm abdominal'.mp.
2 '##'Stent$'.mp.##'/ or Stents/ or 'stent$'.mp.
3 Blood vessel prosthesis/ or 'blood vessel prosthesis'.mp.
4 'RANDOMISED CONTROLLED TRIAL'.mp.
5 Meta-analysis/ or 'meta-analysis'.mp.
6 Controlled clinical trials/ or 'controlled clinical trial'.mp.
7 'CLINICAL TRIAL'.mp.
8 '##'Random$'.mp.##'/ or Random allocation/ or 'random$'.mp.
9 (meta-anal$ or metanalys$ or meta analy$).mp. [mp=title, abstract, registry number word, mesh subject heading]
10 ((doubl$ or singl$) and blind$).mp. [mp=title, abstract, registry number word, mesh subject heading]
11 exp Clinical trials/
12 Cross-over studies/
13 1 and (2 or 3)
14 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
15 13 and 14

Search for systematic reviews

1 exp aortic aneurysm, abdominal/ or 'aortic aneurysm abdominal'.mp.
2 '##'Stent$'.mp.##'/ or Stents/ or 'stent$'.mp.
3 Blood vessel prosthesis/ or 'blood vessel prosthesis'.mp.
4 Meta-analysis/ or 'meta-analysis'.mp.
5 (meta-anal$ or metatanalys$ or meta analy$).mp. [mp=title, abstract, registry number word, mesh subject heading]
6 'REVIEW'.mp.
7 exp classification/ or 'systematic'.mp.
8 4 or 5 or 6 or 7
9 1 and (2 or 3)
10 8 and 9

Search for cost and health economic information

1 exp aortic aneurysm, abdominal/ or 'aortic aneurysm abdominal'.mp.
2 '##'Stent$'.mp.##'/ or Stents/ or 'stent$'.mp.

3 Blood vessel prosthesis/ or 'blood vessel prosthesis'.mp.

4 1 and (2 or 3)

5 Costs and cost analysis

6 4 and 5

However, these strategies were not sufficiently sensitive to locate known studies of relevance. Therefore, the trials chosen for study were selected from those articles found using the initial search strategy. In addition, two key articles[38,39] were identified from references in other articles, and were not located by any of the above search strategies.

Other sources searched were:

- Cochrane library;
- CRD (DARE/NEED/HTA databases).

6. RESULTS

6.1 Quantity and Quality of Research Available

6.1.1 Evidence for the Use of Endoluminal Repair rather than Open Repair or Conservative Treatment

Many articles have been published which describe the use of endoluminal stent-grafts in individual cases or in case series. However, comparative studies are few. Only one published randomised trial was found which compared ER with a different treatment modality, in this case conventional open repair.[40] Two additional randomised trials compared specific aspects of ER: the relative merits of dacron and PTFE prostheses,[41] and the degree of inflammatory reaction following the implantation of two different types of sealed vascular prosthesis.[42]

A further eight studies were found which compared ER with either open repair or conservative treatment. Two of these only compared endoluminal and open repair in terms of short-term biological responses rather than longer-term outcomes.[43,44]

Those studies were selected for review, therefore, which compared ER with another form of care (either open repair or no treatment), and which made that comparison in terms of mortality and either morbidity or cost (for details, see Table 5). One study[40] reported the experiences of three separate groups of patients, only one of which was involved in a comparative trial. Only the results of that trial, which randomised patients to ER or standard open repair, are discussed here.

One study specifically selected patients with aneurysms where the maximum diameter was 50mm.[45] The remainder all involved patients with aneurysms where the mean maximum diameter was between 50 and 60mm.

Table 5 Studies Selected for Discussion

Authors and Publication Date	Date Endoluminal Procedures Undertaken	Number of Patients		Mean Patient Age (Years)		Mean Aneurysm Size (mm)		Endograft Configuration	Comparison With:	Length of Follow-up
		Control	ER	Control	ER	Control	ER			
White et al. 1996[46]	May 1992-Nov 1994	27	34	68.7	69.0	55	52	Tube (22) Bifurcated (2)	Open repair	Not stated
Edwards et al. 1996[40]	June-Sept 1994	4	4	65.3	68.3	65	65	Tube (4)	Open repair	15 months (mean)
May et al. 1998[38]	May 1992-May 1996	195	108	69	70	56	53	Tube (48) Bifurcated (35) Aorto-iliac/ Femoral (25)	Open repair	34 months (median)
May 1997[45]	June 1992-Aug 1996	67	43	71.4	69.6	41	44	Tube (26) Bifurcated (12) Aorto-iliac (5)	Watchful waiting	22 months (mean)
Brewster et al. 1998[47]	Jan 1994-May 1997	28	30	73.9	75.8	55	55	Tube (8) Bifurcated (8) Aorto-uni-iliac (12)	Open repair	11 months (mean)
Hölzenbein et al. 1997[39]	Feb 1995-March 1996	22	22	69.5	70.1	56	53	Tube (10) Bifurcated (12)	Open repair	9 months (median) in ER group
Makaroun et al. 1998[48]	Feb 1996-Feb 1998	69	50	71	72	59	56	Tube (15) Bifurcated (31) Aorto-iliac (4)	Open repair by the same surgeon	7.5 months (mean)
Zarins et al. 1999[49]	18 month period – probably 1996 - 1997	60	190	69	73	56	56	Medtronic AneuRx Stent Graft	Open repair	12 months

6.2 Evidence for Effectiveness

If a successful ER is defined as a graft placement without early or late conversion to open repair, graft occlusion or persistent endoleak, these studies suggest a technical success rate for ER of around 75-80%. When peri-operative mortality is taken into account, the overall success rate falls to around 70-80% (see Table 6).

Peri-operative mortality, at 0-6% for ER, appears similar to (but usually lower than), that for open repair (0-14%). Lower too is the rate of systemic/remote complications (i.e. medical complications, such as, renal insufficiency, cardiac failure and stroke, which are related to the patient's general medical condition).[50] These stand at 0-29%, compared with 0-64% for open repair (see Table 6). The most recent (third) RETA report is suggesting similar mortality rates for ER when compared to the mortality rates of open repairs in the same units.

ER appears to carry a higher rate of local/vascular complications (i.e. complications directly related to the method of AAA repair, such as, damage to arteries, graft stenosis and groin wound complications)[50] than does open surgery (19-57% compared with 0-15% - see Table 6). Moreover, these rates will rise if immediate conversion to open repair is included as such a complication rather than a planned back-up manoeuvre.[46] However, if conversion to open repair is excluded, the local/vascular complications associated with ER tend to be less severe than the systemic/remote complications which predominate in open repair.[47]

6.3 Quality of the Research

The quality of the studies on which these conclusions are based is not good. The weaknesses included both weaknesses of design and of reporting. Moreover, in general, uncontrolled, non-randomised observational studies are associated with an over/under-estimation of treatment effects which may be suggested through fully randomised controlled trials.[51] When using observational study evidence, conclusions can be drawn using statistical comparisons, such as meta-analysis; however, such methods carry dangers in terms of confounding factors and study bias.[52]

Table 6a Outcome Measures: Mortality, Complications and Success Rates

Study	White et al. 1996[46]		Edwards et al. 1996[40]		May et al. 1998[38]		May et al. 1997[45]		Brewster et al. 1998[47]	
	Control	ER	Control	ER	Control	ER	Control	ER	Control	ER
Immediate/ very early conversion to open repair	Not applicable	18% (6/34)	Not applicable	0% (0/4)	Not applicable	12% (13/108)	17% (11/65) 4 open and 7 ER because of aneurysm growth	14% (6/43)	Not applicable	7 (2/30)
Peri-operative mortality	3.7% (1/27)	0% (0/34)	0% (0/4)	0% (0/4)	6% (11/195)	6% (6/108)	1.5% (1/65) (1 death from aneurysm rupture)	5% (2/43)	0% (0/28)	0% (0/28)
Local/vascular complications	15% (4/27)	25% (7/28)	0% (0/4)	50% (2/4)	9% (17/195)	26% (28/108)	Not applicable	19% (8/43)	7% (2/28)	57% (16/28)
Systemic/ remote complications	37% (10/27)	29% (8/28)	0% (0/4)	0% (0/4)	20% (38/195)	18% (18/108)	Not applicable	23% (10/43)	64% (18/28)	14% (4/28)
Late complications	Not stated	Not stated	0% (0/4)	25% (1/4)	0.5% (1/195)	6% (6/108)	Not applicable	7% (3/43)	Not stated	18% (5/28)
Late conversion to open repair	Not applicable	7% (2/28)	Not applicable	25% (1/4)	Not applicable	6% (7/108)	Not applicable	0% (0/43)	Not applicable	7% (2/28)
Early + late conversion	Not applicable	23% (8/34)	Not applicable	25% (1/4)	Not applicable	19% (20/108)	Not applicable	14% (6/43)	Not applicable	13% (4/30)
Patients free of complications	55% (15/27)	57% (16/28)	100% (4/4)	50% (2/4)	Not stated	Not stated	Not applicable	Not stated	54% (15/28)	50% (14/28)
Technical success rate*	Not stated	76% (26/34)	100% (4/4)	75% (3/4)	99% (194/195)	77% (83/108)	Not applicable	79% (34/43)	Not stated	77% (23/30)
Success rate**	Not stated	76% (26/34)	100% (4/4)	75% (3/4)	94% (183/195)	71% (77/108)	Not applicable	74% (32/43)	Not stated	77% (23/30)

* i.e. graft successfully placed using intended technique (in the case of ER, without late conversion to open repair or persistent endoleak)

** i.e. graft successfully placed using intended technique without death within 30 days of implantation and, in the case of ER, without late conversion to open repair, graft occlusion or persistent endoleak

Table 6b Outcome Measures: Mortality, Complications and Success Rates (cont'd)

	Hölzenbein et al. 1997[39]		Makaroun et al. 1998[48]		Zarins et al. 1999[49]	
	Control	**ER**	**Control**	**ER**	**Control**	**ER**
Immediate/ very early conversion to open repair	Not applicable	0% (0/22)	Not applicable	6% (3/50)	Not applicable	0% (0/190)
Peri-operative mortality	14% (3/22)	0% (0/22)	0% (0/69)	2% (1/50)	0% (0/60)	3% (5/190)
Local/vascular complications	Not stated	Not stated	Not stated	40% (20/50)	12% (7/60)	9% (16/190)
Systemic/ remote complications	Not stated	Not stated	Not stated	4% (2/50)	12% (7/60)	3% (6/190)
Late complications	Not stated	Not stated	Not stated	14% (7/50)	Not stated	Not stated
Late conversion to open repair	Not applicable	Not stated	Not stated	0% (0/50)	Not applicable	0% (0/190)
Early + late conversion	Not applicable	Not known	Not applicable	6% (3/50)	Not applicable	0% (0/190)
Patients free of complications	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Technical success rate*	Not stated	Not stated	Not stated	80% (40/50)	98% (59/60)	77% (146/190)
Success rate**	Not stated	Not stated	Not stated	78% (39/50)	77% (46/60)	78% (146/190)

* i.e. graft successfully placed using intended technique (in the case of ER, without late conversion to open repair or persistent endoleak)

** i.e. graft successfully placed using intended technique without death within 30 days of implantation and, in the case of ER, without late conversion to open repair, graft occlusion or persistent endoleak

Some of the weaknesses of design were inevitable, given the desire to share information about the new procedure sooner rather than later. These appear to have affected all the studies, and include:

- comparing a new technique involving a range of early prototype devices with an established surgical technique;[46,53]

- inadequate length of follow-up.

Of these, the latter is perhaps the more problematic since it may lead to unrealistic expectations for the procedure. In none of the studies was the length of follow-up sufficient to allow all late complications to emerge and the long-term success of the procedure to be estimated. The study, of patients who had undergone ER with the longest duration, had a median follow-up of 29 months.[54] This is particularly problematic, since it is not yet known whether the dilatation of the proximal aortic neck at the site of proximal device fixation (which accompanies the reduction in diameter of the aneurysmal sac brought about by successful AAA exclusion) is progressive and whether, if so, it results in device migration with subsequent endoleakage.[24] Moreover, the durability of the devices, and the most successful means of attachment given the possibility of changes in arterial size over time, are, as yet, unknown.[24,40]

In addition to the above weaknesses of design, two teams[48,54,55] acknowledge a problem which is likely to have affected all, namely the relative inexperience of the clinicians involved in endoluminal techniques. The potential impact of this is indicated by one team which notes that both of the peri-operative deaths and four out of six conversions to open repair occurred early in the course of their study, and attributes this to the learning curve for the new technique;[55] the same team found that the primary conversion rate fell from 20% to 8% as they gained experience.[54]

Another weakness, which appears to affect all the studies which compare endoluminal with open repair, was not inevitable. This is the more intensive follow-up of the endoluminal group, which made it more likely that any failures or complications would be discovered in these patients than in those who underwent open surgery. Indeed, two studies compared prospectively recorded data for ER with retrospectively analysed data for open repair, and their authors note that this may have led them to

underestimate the incidence of complications for open repair.[46,54] Blinding of outcome assessors to treatment allocation, if feasible, does not appear to have been attempted in any of the studies.

It may be seen, then, that one of the biases introduced by the various weaknesses of study design (inadequate length of follow-up) favours, and others (newness of the technique, relative inexperience of the clinicians, more intensive follow-up of the intervention group) disadvantage, ER.

Many of the studies also include weaknesses of reporting, which introduce bias which would appear to favour open repair. Four of the six studies, which compare ER with open repair, do not provide as much information about the outcomes of the latter as the former, often failing to provide comparable information on complication rates and appearing to assume that open repair invariably results in successful graft placement. Other studies suggest that this is not necessarily so. Although the success rate of conventional surgery is high, in excess of 93%,[24] it may have a late complication rate as high as 2%.[18] Four out of six studies, however, fail to comment on the late complication rate in this group (see Table 6).

One study did not use intention to treat analysis,[47] whilst another, which states that it did, does not report the data in this format.[46]

In addition, one of the studies[48] presents information relating to the group of patients undergoing ER in such a manner that some uncertainty attends the data summarised in Table 6 on complications in patients from this study undergoing ER.

6.4 Generalisability of Trial Results

The generalisability of the trial results is uncertain because of the highly specialised nature of the procedure involved, which argues for its concentration in a limited number of centres. The training required to perform ER is considerably different from, and more intensive than, that for conventional surgical repair. Following training, endoluminal procedures must be carried out frequently and regularly to maintain individual and team proficiency.[30] However, as two teams comment on their initial

relative inexperience in endoluminal techniques,[48,55] it may be that comparable results could be achieved elsewhere on comparable patient groups.

A more serious problem in terms of generalisability is the fact that ER is generally considered an attractive option for patients who are at high risk for surgery. However, the majority of the above studies took as their subjects patients who were suitable for open surgery. In only two studies was suitability for surgery not a condition of enrolment. One of these[55] compared ER with conservative treatment. This left only one[54] which compared ER in a population 44% of whom were unsuitable for open surgery with open repair within a population which was suitable for surgery. This is also the study which reports the lowest overall success rate (although, given the small numbers treated in some of the other studies, this may not be statistically significant). Therefore, it is possible that less favourable results will be obtained if ER is used to treat increasing numbers of patients at high risk for open repair.

Moreover, the endoluminal devices currently available are likely to be better than those used in the studies discussed above. One team states that four out of six conversions to open repair occurred with devices which are now superseded.[53] In addition, more recent devices may be introduced using smaller, more flexible access sheaths, and this is likely to reduce the incidence of vascular complications.[53]

6.5 Outcomes

6.5.1 Benefits of Endoluminal Repair

Potential benefits which have been claimed for ER in comparison with open repair include the reduction of post-operative morbidity and pain, less compromise of gastrointestinal function, earlier return to normal diet, improved respiratory function, earlier mobilisation and earlier return to normal activity.[46] Only one of the studies reviewed above[47] includes in its list of outcomes the time taken from hospital discharge to return to a feeling of pre-operative well-being. Some of the other studies address this benefit indirectly in terms of factors such as mean operative time, blood loss, length of ITU stay, and length of hospital stay. This information is summarised in Table 7.

These benefits assume that ER is used in patients who would otherwise have undergone open repair. However, it could be argued that, when complication rates are taken into account, the benefits of ER are relatively slight for patients who are suitable for open repair, and that the real benefit of ER is that it enables patients who would not have been suitable for surgery to undergo aneurysm repair.

6.5.2 Disbenefits

Of those who are suitable, a significant proportion will require conversion to open repair either immediately or at a later date; the studies reviewed here suggest that this proportion may be as high as 25% (see Table 6). Converting an endoluminal procedure to open repair is often technically more complicated than a standard open repair and, therefore, may result in a high morbidity and mortality rate - one study indicated a mortality rate of 17%. While the risk of requiring conversion is equal in all patients, whether or not they were originally considered suitable for open repair, perhaps unsurprisingly the risk of death as a result of conversion for patients originally rejected for open repair because of comorbidities appears to be as high as 43%.[56]

A number of complications are associated with ER, one of the most serious of which is renal impairment. However, only that complication which is most directly attributable to ER, and which is perhaps the most common complication of such repair, endoleakage, is discussed here. Persistent endoleaks have been shown to be correlated with AAA expansion and possibly rupture. The reported occurrence of early endoleak ranges from 10% to 44% and, although as many as 50% of these may seal spontaneously weeks or months after endograft implantation, some of these apparently self-correcting leaks may recur later.[47] Because of the relatively short follow-up period in the reported studies, it is not known how many patients will ultimately require further endoluminal procedures or conversion to open repair as a result of recurring endoleaks.

It has also been suggested that, if conventional open repair is required following ER, this may be more difficult or complex because of that earlier repair.[47]

Table 7a Outcome Measures: Operative Time, Blood Loss, Length of ITU and Hospital Stay

Study	White et al. 1996[46]		Edwards et al. 1996[40]		May et al. 1998[54]		May et al. 1997[55]		Brewster et al. 1998[47]	
	Control	ER	Control	ER	Control	ER	Control	ER	Control	ER
Mean operative time (hours)	2.58	3.1	2.4	2.3	Not stated	Not stated	Not applicable	Not stated	3.52	3.25
Mean blood loss (ml)	1,422	873	Not stated	Not stated	1,271	556	Not applicable	Not stated	1287	498
Mean units of blood transfused	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not applicable	Not stated	Not stated	Not stated
Mean length of ITU stay (days)	1.8	0.7	Not stated	Not stated	2.1	0.8	Not applicable	Not stated	1.75	0.1
Mean length of hospital stay (days)	12.4	11.1	5.3	1.8	11.7	10.5	Not applicable	Not stated	10.3	3.9
Mean time from hospital discharge to return of a feeling of pre-operative well-being (days)	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not applicable	Not stated	47	11

Table 7b Outcome Measures: Operative Time, Blood Loss, Length of ITU and Hospital Stay (cont'd)

Study	Hölzenbein et al. 1997[39]		Makaroun et al. 1998[48]		Zarins et al. 1999[49]	
	Control	ER	Control	ER	Control	ER
Mean operative time (hours)	3.82 (median time)	3.47 (median time)	Not stated	3.0*	3.6	3.1
Mean blood loss (ml)	Not stated	Not stated	Not stated	212**	1596	641
Mean units of blood transfused	2.73	0.55	Not stated	Not stated	1.6	0.3
Mean length of ITU stay (days)	2.29	0.95	Not stated	Not stated	2.5	0.9
Mean length of hospital stay (days)	22.8***	14.9***	5.9	2.5****	9.4	3.4
Mean time from hospital discharge to return of a feeling of pre-operative well-being (days)	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

* Mean time for the successful procedures; mean time for the 3 which needed immediate conversion to open repair was 6.1
** For the successful procedures; 2,866 for the 3 which needed immediate conversion to open repair
*** Includes admissions for pre-surgical testing averaging 3.0 days in the control group and 7.2 days in the ER group
**** For the successful procedures; 3.2 including those which needed immediate conversion to open repair.

6.6 Conclusions about Outcomes from Endovascular Abdominal Aortic Aneurysm Repair

A number of comparative, but non-randomised, studies were identified which showed that endoluminal AAA repair has a lower peri-operative mortality rate than open repair; a further study compared ER with watchful waiting. Four studies suggested that ER had a lower rate of systemic/remote complications than open repair, but four showed that it had a higher rate of local/vascular complications. Peri-operative mortality was similar for each type of intervention, but longer-term outcome comparisons are still largely unknown. The overall success rate of ER (i.e. successful placement, no endoleak and without mortality by 30 days) was between 70-80%; between 6-25% of patients had to undergo immediate or late conversion to open repair.

6.7 Economic Analysis

The literature search found no published papers reporting formal cost-effectiveness or cost-benefit analyses comparing ER with either open repair or more conservative medical treatments. Ideally, the authors would like to be able to calculate costs per quality adjusted life year (QALY) ratios for these alternative treatment regimens. The choice of alternative treatments depends upon the patient groups being analysed and, specifically, whether or not patients are fit or suitable for open surgery. The lack of published evidence about the longer term benefits of ER and the constantly changing stent technology, makes any economic evaluation of ER particularly difficult at this time.

6.7.1 Estimation of Net Benefits

The benefits of ER of AAA depend upon the patient groups being treated. Four patient groups can be defined: -

- Patients unsuitable for ER;
- Patients fit for either open repair or ER;
- Patients unfit (or unsuitable) for open repair;
- Patients with small aneurysms.

Patients unsuitable for ER (e.g. for anatomical reasons) are not affected by the advent of endovascular treatment and, therefore, are not considered further here.

Key benefits to the group fit for either type of surgical intervention include the short-term advantages of a less invasive procedure. The long-run benefits in terms of life years gained and QALYs are uncertain and will depend on factors such as the peri-operative and longer-term complication rates (e.g. endoleaks, subsequent re-operation, and ruptures) and mortality rates associated with the two procedures. The benefits to fit patients are the subject of the Endovascular Aneurysm Repair (EVAR)1 clinical trial.

The benefits to unfit patients are clearer in that an operative procedure is now available to a group previously unfit for surgical intervention. Consequently, there is clear potential for extending life for those patients who would otherwise die early from a ruptured aneurysm. The net benefit in terms of life years gained will depend on the trade-off between the short- and longer-term risk of endoluminal surgery, versus the risk of death from rupture, when there is no elective operative intervention. The latter will in turn be dependent on aneurysm expansion rates. Other things being equal, the relative life expectancy for the unfit group of patients will be lower than for the general population. As such, the life years gained from endoluminal intervention can be expected to be relatively low. The benefits to unfit patients are the subject of the EVAR2 clinical trial.

The relative benefits of endovascular surgery for patients fit, but unsuitable, for open repair (e.g. because of a hostile abdomen) will be similar to those in the unfit group except that in general, this group of patients will have a longer life expectancy than the unfit patients. Consequently, there is potential for greater life years gained from the endoluminal procedure for this patient group. This group of patients is not explicitly part of the EVAR trials.

The benefits for the small aneurysm group are particularly uncertain. The UKSAT concluded that elective open repair was an unnecessary intervention for aneurysms smaller than 55mm in diameter. It needs to be established whether (or by how much) reductions in the short- and long-term risks from endovascular surgery can make the intervention a cost-effective alternative to conservative treatment for the small aneurysm patient group.[12]

Consequently, the benefits of ER in terms of additional life years gained (quality adjusted or not) are very uncertain at this point in the development of the technology. The benefits to patients will also vary by patient group. A modelling exercise and/or the results of the EVAR trials should help to inform the current uncertainties around the benefits of this relatively new intervention.

6.7.2 Estimation of Net Cost

NHS costs of the new endoluminal procedure

There are substantial direct costs associated with ER compared with open repair, namely:

- Additional screening tests are required to determine whether the patient is anatomically suitable for ER;[39]

- The stented endografts used are all more expensive than standard vascular grafts, and additional endovascular instruments (guide wires, balloon catheters and special task catheters) are also required;[39]

- To allow for immediate conversion to open repair, if necessary, ER must be undertaken in an operating theatre, which must also be equipped with the state-of-the-art imaging systems required for ER. This may require major investment.[18,39] The need for conversion will be dependent on patient selection criteria.

- The cost of follow-up is greater than for standard repair because of the need for additional radiological examinations.[39]

The longer-term costs for ER are uncertain because of the uncertainties surrounding the longer-term complication rates for the procedure, particularly the endoleak rates and the likely need for further surgical intervention for endoleak repair. Moreover, the constantly improving stent technology will influence both the longer- and shorter-term success of the intervention. These technological changes and the lack of longer-term follow-up evidence for endoleak repair make it particularly difficult to assess the true marginal opportunity cost for this procedure.

In addition, as ER can also be used to treat patients at high risk from open repair, the number of patients with AAA who undergo aneurysm repair may rise and, therefore, the overall costs of the service will increase. On balance, it seems reasonable to expect that treatment costs for such patients will be higher than those for fitter patients, given that complication and open conversion rates are likely to be higher for unfit patients. Balancing this, however, is the potential reduction in ruptured aneurysms - the costs of emergency

repair were estimated at £10,500 by the UKSAT team.[12] This figure is more than double their estimate of the costs for elective repair.

NHS Savings from the New Endoluminal Procedure

ER can lead to cost savings associated with reductions in ITU and hospital stays compared with open repair.[39] Those studies which provided the relevant information stated that ITU stay was more than halved in patients undergoing endoluminal compared with open repair (see Table 7). The study which reported the longest ITU stay for patients undergoing ER[39] noted that this was due to the ethics committee's requirement that these patients should undergo special surveillance in an ITU for at least 12 hours, and that none of them required ITU admission for medical reasons; in the same study, the group undergoing open surgery was not routinely admitted to ITU.[39]

In addition to the reduction in ITU stay, all of the studies reported a reduction in hospital stay in those patients who underwent ER (see Table 7). However, in some cases the reduction was relatively small (around 10%). In one such case, the authors stated that length of hospital stay for patients undergoing ER was influenced by the fact that they were often kept in hospital for extra days to observe for known and unknown complications, because the procedure was so new, and to allow for complete follow-up imaging, rather than strictly for medical indications.[46] In another instance, although the mean length of hospital stay for ER was substantially shorter than that for open repair, it was, nonetheless, longer than in any of the other studies, and was protracted because the local, Austrian, reimbursement policy encouraged the performance of the entire pre-operative evaluation on an in-patient basis. However, the post-operative length of stay (averaging 13.3 days for open surgery and 5.6 days for ER) was said to be comparable with that reported in the literature.[39] Moreover, this study noted that all patients who had undergone ER were discharged home, but that some of those who had had open repair were transferred to other hospitals or secondary care facilities.[39] It seems likely, therefore, that, as the technique becomes established, the average length of stay of patients undergoing successful endoluminal graft implantation may well be less than half that of similar patients undergoing open repair. However, as noted above, two of the studies exclude from their published analysis those patients who had to undergo immediate conversion to open repair, and the difference between endoluminal and open repair in terms of average lengths of stay, based on an intention to treat analysis, is likely to be less favourable to ER.

Net Costs

The costs of the ER procedure itself have been estimated to be almost three times higher than the procedural costs for open surgery - 10,700 ECU (£8,560 using ECU = £0.8 exchange rate) versus 4,032 ECU (£3,225). These figures are in 1996 currency and are for patients considered fit for both types of procedure. The costs of the radiological testing were estimated to be five times higher for endoluminal compared with open procedures.[39]

Hölzenbein has estimated the total cost of the whole intervention to be 25,374ECU (£20,300) for open repair and 22,269 ECU (£17,815) for ER.[39] This is a 14% difference in favour of ER. The reduced costs are a result of a faster patient recovery associated with a shorter length of hospital stay. The Hölzenbein analysis is unsatisfactory in a number of ways, however. The sample size of 44 is small and atypical in that no patients required conversion from endovascular to open repair. The latter biases the results in favour of ER. Indeed, another study found that, when the cost of failed, as well as successful, ER was taken into account, the cost of the device and interventional supplies used during the procedure almost exactly offset the cost savings derived from the reduction in hospital stay.[48] On the other hand, as discussed above, hospital and ITU lengths of stay were longer than necessary. Also, tertiary sector care costs were excluded from the analysis. Both these effects bias the results against ER.

The UKSAT[12] has enabled a comparison of the NHS costs and benefits of surgical versus a more conservative regimen involving radiological assessment.[12] The analysis indicates that for aneurysms of 40-55mm diameter the conservative 'watch and wait' regimen is cheaper than early surgical interventions over a wide range of assumptions (£5,000 versus £4,000 at 1996/97 prices using a 6% discounting rate). The cost of ER was estimated at £6,800, though this figure is calculated using only a small sub-group of the whole trial population (12/1,090). In contrast to the Hölzenbein results, this UK study indicates a higher cost for endovascular compared with open repair, although the costs of both procedures are considerably less than those estimated in Austria. Having said this, the UK estimate for the endovascular costs did use the unrepresentative ITU length of stay data from the Austrian study, which will have increased the estimated costs for this procedure. Jepson[57] has estimated the cost of elective AAA repair at £4,600 (1993 prices) in Scotland. Allowing for inflation, this is a similar figure to that reported by the UKSAT.

Using a bottom-up costing approach with information provided by Sheffield's Northern General Hospital, some costs have been estimated for the repair of AAA. Making

assumptions about the device costs, theatre time, and post-operative (High Dependency Unit (HDU)/ITU and ward stays and per diem costs), the costs of the ER are estimated to be circa £7,500 for a fit patient and £8,300 for an unfit patient. The costs for an elective open repair are similarly estimated to be circa £6,300 for a fit patient. Most of the EVAR cost relates to the device and consumables (£5,000), whereas most of the cost of the elective open repair relates to the ITU and ward stays (£6,200). The costs of an emergency open repair of a ruptured aneurysm have been estimated at £6,500 for those patients not surviving the operation and £13,000 for the small percentage of survivors.

Thus, there are a number of estimated costs and savings for endovascular and open elective and emergency repair of AAAs. These derive from a variety of published and unpublished sources, from different healthcare contexts, and for different patient types. Therefore, their use and comparison should be treated with caution. The published estimates for the costs of an endovascular procedure are particularly uncertain, ranging from 14% less to 20% more than open repair. The endovascular procedure costs are particularly difficult to estimate given that the stent technology is still in a developmental stage, so that the procedure costs and the operative and post-operative complication rates are constantly changing. The sensitivity of the costings to realistic ITU and overall hospital bed utilisation makes it hard to give an overview at this stage. Perhaps the best one can say is that the ER and elective open repair procedures cost similar amounts. Ignoring the benefit implications from life years gained or lost, emergency open repair of ruptured AAA can cost considerably more than the elective procedures.

6.7.3 Estimation of Cost-effectiveness and/or Cost Utility

There are no published papers reporting a formal economic analysis of endovascular AAA repair comparing it to either open repair or conservative management. Three patient groups have been identified for whom the cost-effectiveness of ER needs assessing. The cost-effectiveness will differ by patient group, as will the available alternative treatments.

- Patients unfit (or unsuitable) for open repair who could undergo the less invasive endovascular procedure rather than waiting for an emergency repair of a ruptured aneurysm, which carries a high risk of pre- or peri-operative death and higher costs. Key variables are likely to be the rupture rate for the untreated group and the mortality rates for this relatively unfit group.

- Those patients fit for either elective open repair or ER. For such patients the authors were interested in modelling the comparative costs and benefits (long-term survival for example) of the two procedures.

- Those patients with small aneurysms. Evidence from the small aneurysm trial indicates that early open surgery is not as cost-effective as conservative management using radiological watchful waiting. Assuming that this finding is accepted as good practice, it now needs to be established how the cost-effectiveness of the endoluminal procedure compares with that of conservative management.

Ideally, the authors are interested in measuring the marginal costs per QALY gained. Due to the lack of published evidence and the constantly improving technology surrounding endovascular stenting, there are significant areas of uncertainty and ignorance particularly about long-term success (e.g. in terms of endoleakage) and survival rates for the endoluminal procedure. As such, the authors are reluctant to comment here on the relative cost-effectiveness of ER of AAA. A decision analysis modelling approach could help to identify threshold values for key variables identifying the points at which endovascular surgery would become a cost-effective option compared with a named alternative for the various patient groups identified above. Two of the authors of this paper (Thomas and Calvert) are currently undertaking cost-effectiveness analyses of ER of AAA using decision analysis and Markov modelling. The results of this work are expected to be submitted for publication in 2000 and will consider the above patient groups. Sensitivity analysis during the modelling process should enable the estimation of relevant threshold values for key variables, and could help identify which variables the EVAR trials should focus their efforts, in terms of obtaining more accurate estimates. In the light of the conclusions and recommendations of this Guidance Note, the scope of this modelling work was considered to be beyond the remit of this report. Early results from this modelling work analysing the cost effectiveness of ER for the unfit and unsuitable patient groups have been made available during the final drafting of this paper. The results indicate that ER is likely to have favourable cost-effectiveness in terms of life years gained for both the unfit and particularly the ‘fit but unsuitable’ for open repair groups of patients. Results are not currently available for the fit patient groups.

7. IMPLICATIONS FOR OTHER PARTIES

This report has raised a number of important issues, which have implications for other parties, both in respect of this specific procedure and clinical area, and more widely in the introduction of new health technologies. These issues are listed below:

- With the advent of Clinical Governance, are there lessons to be learned from the introduction of stents, the Safety and Efficacy Register of New Interventional Procedures (SERNIP), (see Appendix A), and the Registry for Endovascular Treatment of Aneurysms (RETA)?

- What mechanisms are in place in Trusts to oversee the introduction of new procedures before they come to the notice of SERNIP (cf. ethics committees for research proposals)? Is there any guidance on obtaining patient consent?

- Registration with RETA is voluntary, and has been incomplete for a number of reasons, not least resources for the registration process.

- RETA has had difficulty in obtaining the co-operation of device manufacturers (except for two) in establishing a parallel register of devices supplied as a means of validating RETA.

- There appears to be a two tier regulatory system, with device manufacturers being subject to far less stringent regulations than drug manufacturers.

- There is a well recognised path of drug development: laboratory, animal and three phases of human studies. Could a parallel path be established for devices?

8. EQUITY ISSUES

Circulatory disease has been selected as one of the four target areas in the recent White Paper 'Saving Lives: Our Healthier Nation'.[58] This area has been included because, amongst other reasons, there are substantial inequalities in health in this disease area. Implementation of improved care to prevent adverse effects from aortic aneurysms must ensure that relevant treatment reaches all population groups in an equitable manner, as there is evidence that other interventions in respect of circulatory disease have not always reached those with greatest need in more deprived areas.[59]

9. OTHER UNQUANTIFIABLE FACTORS

Perhaps the main opportunities for prevention are in the reduction of cigarette smoking and good control of hypertension – it is unclear at present how much impact past, current and future initiatives in this area will have on the epidemiology of AAAs.

10. OPTIONS FOR PURCHASERS/COMMISSIONERS

Three main options present themselves for purchasers/commissioners of health services:

1. Do not change current contracting arrangements.

2. Purchase endovascular AAA repair only in the context of the current trials (notably EVAR1 and 2).

3. Purchase for patients deemed clinically suitable, but insist that centres undertaking these procedures provide clear audit results of their outcome and participate in the RETA database.

11. CONCLUSIONS

11.1 Main Results

A number of comparative, but non-randomised, studies were identified (taken together, a total of nearly 1,000 patients, split between either endoluminal or open repair, were included). These showed that endoluminal AAA repair has a lower peri-operative mortality rate than open repair; a further study compared ER with 'watchful waiting'. Four studies suggested that ER had a lower rate of systemic/remote complications than open repair, but four showed that it had a higher rate of local/vascular complications. Peri-operative mortality was similar for each type of intervention, but longer-term outcome comparisons are still largely unknown. The overall success rate of ER (i.e. successful placement, no endoleak and without mortality by 30 days) was between 70-80%; between 6-25% of patients had to undergo immediate or late conversion to open repair.

It is possible that, after the initial outlay involved in equipping theatres to undertake ER, the procedure may be no more expensive than open repair. However, if the procedure is used to increase the number of patients undergoing aneurysm repair, the overall costs of the service will rise, perhaps substantially.

11.2 Assumptions, Limitations and Uncertainties

The design of the studies was variable. Some had specific flaws as discussed above. The lack of long-term follow-up is particularly worrying. The generalisability of the results is questionable given the limited inclusion criteria, with most of the studies only recruiting patients suitable for open surgery.

11.3 Need for Further Research

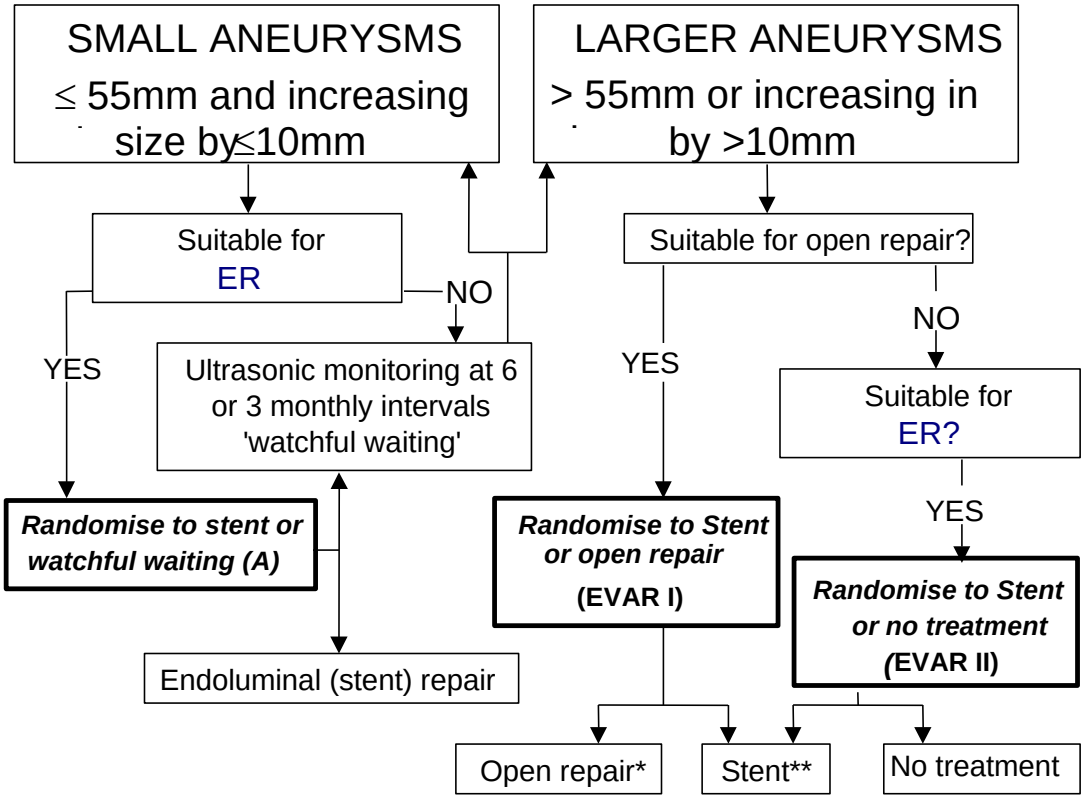
Further research is needed to assess the long-term effects of endoluminal aneurysm repair. While it may appear that there is little to lose in undertaking such repair in patients who are not suitable for open repair, it has been suggested that prospective randomised studies with follow-up for at least five years will be required to determine the potential role of endoluminal grafting of AAA in the patient who is fit for conventional open repair.[46]

As discussed earlier, a UK randomised controlled trial (with two components EVAR1 and EVAR2) is planned to start in 1999. It has been delayed many times and there are a number of problems still being raised. In particular, there is a view that the intervention is not yet 'mature' with practitioners still on a learning curve and devices still being modified. The trial design requires that open surgery controls must be operated on and followed up in the same centres as stent cases. Funding arrangements are unclear as workload shifts from district general hospitals to specialist centres and some of these may not have sufficient capacity especially in ITUs.

Two issues must be addressed in addition to the simple comparison with open surgery. *Firstly*, what are the benefits of stents in treating patients unsuitable for open surgery, who contribute disproportionately to the aorto-uni-iliac + crossover group with its necessity for open procedure and higher mortality (RETA)?

Secondly, if death rates for stents are no better than those in open procedures (RETA), and given the results of the Small Aneurysms Trial,[12] will there be any justification for treating smaller aneurysms (<55mm) or, indeed, ethical justification for a trial to find out? Figure 1 illustrates the options for the management of aortic aneurysms expressed as a trial protocol. The planned EVAR trial does not address the issue of stenting small aneurysms ($\leq$ 55mm), yet whether stenting small aneurysms is, or is not, effective and cost-effective is crucial to any debate on the introduction of aneurysm screening.

Figure 1 **Management Options for Asymptomatic Abdominal Aortic Aneurysms: Research Protocol**



Notes:
(A) there is no research planned for this area, but the outcome of such a trial would be crucial to any decision concerning the introduction of screening for aortic aneurysms, as the introduction of a screening programme would be predicated on the existence of an effective and safe intervention.
* These patients are to be operated on at the same centres as the stents arm. This will constitute a shift in activity from DGHs to research centres. Who is to fund this arm? Will DGH surgeons choose not to recruit to the trial to avoid losing open procedures to the trial (thus threatening the trial)?
** Are these to be funded at full cost by the trial or at marginal cost over open repair? If the latter, the financial problems caused by the shift from DGH to centre as above will apply to this arm as well, though more problematic for non-(trial)-host HAs.

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CONFLICT OF INTEREST

None of the authors of this document has any financial interests in the drug or product being evaluated here.

EXPIRY DATE

The conclusions based on this guidance note will need to be revisited when the UK randomised controlled trials mentioned above report. This is expected to be in five years' time.

APPENDIX A Safety and Efficacy Registry of New Interventional Procedures of the Academy of Medical Royal Colleges (SERNIP)

This is the first Trent DEC report covering a topic which has also been reviewed by the Safety and Efficacy Registry of New Interventional Procedures (SERNIP) of the Academy of Medical Royal Colleges. The history of SERNIP is described below along with a list of the procedures it has considered.

It has a small staff and resources and yet has reviewed a wide range of procedures. These resource constraints, along with the desire to be independent of Government/NHS, have meant that the communication of its findings (and indeed, its existence) has not been as effective. It was apparent in 1998 that many Trust Medical Directors and Directors of Public Health were not aware of SERNIP's activity.

The establishment of SERNIP predates the advent of Clinical Governance. Whilst the trigger for Clinical Governance was concern over the delivery of established procedures, some of the principles of Clinical Governance are anticipated by SERNIP. Indeed, it could be argued that unproven/experimental procedures represent a greater potential threat to patients than sub-standard delivery of established interventions. Thus, the importance of SERNIP has increased markedly and this should be reflected in its resources.

Other bodies are responsible for establishing and maintaining registries of activity relating to individual procedures registered with SERNIP. In this case the Vascular Surgical Society of Great Britain and Ireland (VSSGBI) has been running the Registry for Endovascular Treatment of Aneurysms (RETA). Whilst this extensive database has been successfully managed (and resourced) by the VSSGBI, it has been more difficult for individual Trusts to find the resources to collect the large dataset; this has resulted in the incomplete registration of procedures. If decisions are to be made as to the future use of a procedure on the basis of incomplete datasets, then clearly there is considerable scope for major errors. It needs to be recognised that the implications of these registries for staff time may be as great as those required to participate in formal research. The NHS R&D Directorate and Academy of Medical Royal Colleges need to give this topic further consideration.

Cross checks on unregistered cases could be made, e.g. by Trust medical supplies departments keeping records of devices and sharing the data with the relevant registry. Also, manufacturers could be asked to supply similar information, though they may view this

as problematic, compromising commercial confidentiality. The Medical Devices Agency should be asked to consider the problem.

SERNIP

Introduction

In 1993, the Medical Royal Colleges, the Department of Health and the Government were increasingly aware of serious complications and even deaths resulting from what was becoming known as 'keyhole surgery'. The Cabinet Advisory Committee on Science and Technology (ACOST) in a report on 'Medical Research and Health', was critical of the lack of a formal system for gathering information on new procedures and for ensuring that there was a systematic assessment of their safety and efficacy.

The response has been to set up SERNIP in the Academy of Medical Royal Colleges to register new interventions and act as an 'intelligence centre' co-ordinating the experiences of doctors developing new techniques and advising on the need for further research. Being a professional organisation, rather than a government body, it aims to work with medical innovators and instrument suppliers to encourage new developments to a point where they can be shown to be safe and efficacious. It does not attempt to evaluate 'effectiveness' in general use (that is the role of audit) nor economic issues (such as cost-benefit).

The First Year of SERNIP

An office was opened at the Academy of Medical Royal Colleges in May 1996 and an Executive Secretary was appointed to promote links with individual Colleges, specialty organisations, and the various tiers of the NHS R&D Executive.

The Clinical Director took up office in October 1996 and following widespread consultations, established a central place for SERNIP within the global medical community; practitioners, providers, purchasers, research and development, health technology assessment and audit. One particularly fruitful exercise was to recruit the assistance of Local Research Ethics Committees in notifying new procedures to SERNIP.

The Academy appointed Professor Norman MacKay to chair an Advisory Committee consisting of representatives nominated by those Royal Colleges with an interest in SERNIP's initial remit (surgery, gynaecology, radiology and cardiology). The Committee's

inaugural meeting was held in January 1997 and the draft constitution and minutes were presented to the Academy in February. Issues such as 'safety', 'efficacy' and 'new procedures' proved difficult to define in scientific terms, but pragmatic guidelines were proposed to enable the Committee to consider a number of novel interventions. The current Chairman is Professor A G D Maran, President of the Royal College of Surgeons, Edinburgh.

How SERNIP Works

Researchers notify SERNIP of a new technique, citing any published results. SERNIP conducts a search of the Medline and Embase databases and looks for reviews in the Cochrane Library and the many international sources which are available on the Internet. This allows a synthesis to be made of information on the subject, accepting only the hardest scientific evidence and peer-reviewed papers in recognised journals. Personal reviews, conference proceedings and trade publications are not normally acceptable.

They also liaise with the Medical Devices Agency, Medical Research Council, Centre for Reviews and Dissemination, National Co-ordinating Centre for Health Technology Assessment and others.

This synthesis is then submitted to an Advisory Committee of experts nominated by the Royal Colleges who allocate the procedure to one of four categories:

A. Safety and efficacy established, procedure may be used.

B. Sufficiently close to a procedure of established safety and efficacy to give no reasonable grounds for questioning safety and/or efficacy; procedure may be used.

C. Safety and/or efficacy not yet established; procedure requires a fully controlled evaluation and may be used only as part of systematic research:
   i. an observational study in which all interventions and their outcomes are systematically recorded;
   ii. a randomised controlled trial.

D Safety and/or efficacy shown to be unsatisfactory; procedure should not be used.

SERNIP has so far evaluated **76** procedures of which:

22 were in category **'A'**,
10 in **'B'**,
42 in **'C'**
2 in **'D'**.

The 'C' Category

Two-thirds of the procedures so far considered fall within this group. It implies that there are insufficient data to prove, with reasonable scientific confidence, that the procedure is safe or that it achieves what it claims (whether diagnostic or therapeutic) and that further systematic clinical trials are required.

SERNIP then tries to identify one key researcher who will co-ordinate the necessary trials and leaves that person to recruit others to the study: all should work to a standard protocol and collect the same data, leading to a publication. When the results are accepted for publication in a recognised journal, SERNIP will reconsider the procedure and hopefully approve it for general use.

During this development phase, SERNIP might receive enquiries from a health authority or Commissioning Group or Health Insurer as to whether the procedure had been approved. In the case of a 'C' procedure, it would be able to identify those units which were involved in the developmental studies and by implication offer the reassurance that no serious risks had been identified and that the procedure was being employed in a controlled fashion by the workers involved. In other words, it would be sending a signal that it would be appropriate to 'purchase' the procedure from one of the known investigating centres. Conversely, it could not send the same message about a unit which it did not know to be involved in the research project.

Another aspect of the 'C' category relates to research funding. SERNIP hopes that Regional Research and Development Committees and other funding organisations will come to recognise that in awarding a grade 'C' to a procedure, SERNIP, as a responsible medical organisation, has scrutinised it and made a positive recommendation to proceed with research.

The Lessons

Evidence-Based Medicine is here to stay and innovators will, in future, be expected to produce first-grade scientific proof of safety and efficacy.

A procedure of unproven safety and/or efficacy should not be provided outside the clinical trial environment.

There may be medico-legal implications to practising new interventional procedures outside a recognised and approved research programme.

Help is at hand with regard to funding for research and development once a SERNIP category 'C' is awarded.

The medical device industry is aware of the need to progress to an 'A category in order to maximise sales potential; manufacturers and suppliers will have to follow the pharmaceutical companies by promoting and supporting the necessary research.

Co-operation with SERNIP is at present entirely voluntary, but if the profession decides to ignore the opportunity of being co-ordinated and advised by its own (in the form of the Medical Royal Colleges); it is more than likely that some form of statutory regulation system will emerge.

How to Contact SERNIP

The SERNIP office is situated at the Academy of Medical Royal Colleges, 1 Wimpole Street, London, W1M, 8AE
Tel: 0171 290 3917
Fax: 0171 495 2432
Email: nicoletaub@sernip.demon .co.uk

SERNIP CATEGORISATION OF PROCEDURES - from January 1997 to April 1999

Serial No.	Category A
108	Angioplasty of pulmonary artery (balloon)
54	Antireflux fundoplication using laparoscopic approach
25	Embolisation of intracranial arteriovenous malformation
6	Endovascular obiliteration of intracranial aneurysm (balloon)
30	Extracorporeal membrane oxygenation (neonatal)
33	Falloposcopy (linear eversion catheter)
92	Injection of drug into vitreous (Ganciclovir implant)
41	Intraoperative lymphatic mapping
44	Laparoscopic adrenalectomy
53	Laparoscopic closure of perforated duodenum
52	Laparoscopic splenectomy
120	Laser coagulation of ciliary body (endoscopic, diode laser)
17	Laser coagulation of ciliary body (transscleral, diode laser)
105	Peranal excision of lesion of rectum (transanal endoscopic microsurgery)
11	Percutaneous emolisation of coronary artery fistula (coil)
84	Simultaneous pancreas-kidney transplantation
70	Stereotactic ablation of globus pallidus tissue (pallidotomy)
95	Stereotactic ablation of thalamus tissue (thalamotomy)
34	Stereotactic radiosurgery for intracranial arteriovenous malformations
96	Therapeutic selective salpingography: cornual cannulation
98	Therapeutic selective salpingography: tubal cannulation
110	Transperineal prostate brachytherapy
116	Uterotubal constrast sonography
Serial No.	**Category B**
119	Colonic stenting
38	Embolisation of intracranial aneurysm (Guglielmi coil)
24	Endoscopic stapling of pharyngeal pouch
46	Laparoscopic gastroplasty (Lap-Band)
63	Mesh plug repair of inguinal hernia (PerFix)
69	Pallidal deep brain stimulation (Parkinson disease)
107	Percutaneous transintimal arterial recanalisation
94	Thalamic deep brain stimulation (Parkinson disease)
101	Thermal endometrial ablation (Gynecare)
102	Thermal endometrial ablation (Vesta DUB)
117	Vagus nerve stimulation for intractable partial seizures in adults

NB:
Intra-operative lymphatic mapping
****approval of this procedure does not imply that sentinel node excision is a proven satisfactory alternative to level 2 axillary node dissection in breast cancer**

Serial No.	Category Ci
20	Embolisation of uterine artery (fibroids)
121	Endovascular obliteration of intracranial arteriovenous malformation (Guglielmi coil)
49	Excision of pelvic lymph nodes group (laparoscopic)
28	Extracorporeal membrane oxygenation (postneonatal paediatric)
32	Falloposcopy (coaxial catheter)
71	Islet cell transplant
43	Laparo-endogastric surgery
65	Microwave endometrial ablation

67	Non-surgical reduction of ventricular septum
10	Percutaneous prosthetric closure of atrial septal defect (Amplatzer)
109	Percutaneous prosthetric closure of atrial septal defect (ASDOS)
76	Percutaneous vertebroplasty (methyl methacrylate)
79	Pseudomyxoma peritonei (Sugarbaker technique)
50	Pyeloplasty (laparoscopic)
51	Radical laparoscopic hysterectomy
58	Removal of cardiac pacing electrode (laser sheath)
83	Selective peripheral denervation for cervical dystonia (torticollis)
87	Stent placement in the right ventricular outflow tract
89	Subthalamic nuclear stimulation (Parkinson's disease)
90	Subthalamic nucleotomy (Parkinson's disease)
99	Thermal endometrial ablation (Cavaterm)
122	Vagus nerve stimulation for refractory epilepsy in children
Serial No.	**Category Cii**
26	Abdominal aortic aneurysm stenting
5	Autologous chondrocyte implantation of femoral condyle (Carticel)
106	Circular stapling haemorrhoidectomy
45	Colposuspension (laparoscopic)
16	Cystourethropexy (In-tac)
72	Cystourethropexy (Vesica)
21	Endoscopic axillary lymph node retrieval
22	Endoscopic dacryocystorhinostomy (laser)
77	Endoscopic macroplastique injection outlet of female bladder
47	Endoscopic primary repair of inguinal hernia (transperitoneal)
29	Extracorporeal membrane oxygenation (adult)
31	Extracorporeal photopheresis (systemic sclerosis)
82	Implantation neurostimulator electrode spinal nerve root (sacral) - urge incontinence
8	Insertion of carotid artery stent
56	Laparoscopic simple nephrectomy (transperitoneal)
75	Laser discectomy (lumbar)
60	Partial left ventriculectomy (Batista)
104	Splanchnic surgical sympathectomy (thoracoscopic)
55	Total laparoscopic hysterectomy
93	Viscosupplementation for osteoarthritis of knee (Synvisc)
Serial No.	**Category D**
40	Intraoperative blood salvage (Haemocell 350)
97	Therapeutic selective salpingography: guide-wire

SERNIP - CLASSIFICATION OF PROCEDURES

a. Safety and efficacy established; procedure may be used;

b. Sufficiently close to an established procedure to give no reasonable grounds for questioning safety and efficacy; procedure may be used subject to continuing audit;

ci. safety and/or efficacy not yet established; procedure requires a fully controlled evaluation and may be used only as part of systematic research, consisting of an observational study in which all interventions and their outcomes are systematically recorded;

cii. Safety and/or efficacy not yet established; procedure requires a fully controlled evaluation and may be used only as part of systematic research, consisting of a randomised controlled trial and advise the Standing Group on Health Technology accordingly;

d. Safety and/or efficacy shown to be unsatisfactory; procedure should not be used.

APPENDIX B The Medical Devices Agency (MDA)

Within the Medical Devices Agency (MDA), European and Regulatory Affairs (ERA) is responsible for the Agency's regulatory role as the UK's Competent Authority for the European Union Medical Devices Regulations. ERA is implementing and enforcing the Medical Devices and the Active Implantable Medical Devices Regulations, and, in due course, the *In Vitro* Diagnostic (IVD) Directive. ERA appoints and audits Notified Bodies and assesses manufacturers' protocols for clinical investigations with the support of the MDA clinical team. It also issues regular Bulletins on aspects of the new unified regulatory European system and gives advice on other Directives which affect medical devices.

All medical devices in order to be placed on the European market must now carry a C.E. marking (Conformité European). This indicates that the device in question has demonstrated compliance with a number of relevant essential requirements covering safety and performance. Unlike pharmaceutical products, where the Medicines Control Agency is responsible for assessing any pharmaceutical product and its suitability for use right up to the time of placing on the market, placing on the market for medical devices is under the control of third party accreditation bodies known as 'Notified Bodies'. Examples in the UK are BSI and Lloyds of London. A device manufactured and used within a Trust (i.e. by a member of staff) would not be subject to the Regulations. However, if such a device were given (even if free of charge) for use by a clinician in another Trust, it would be subject to the Regulations; the same would be true if manufactured in a University (e.g. its bioengineering department) for use in an NHS Trust.

The MDA does not carry out, commission or consider formal effectiveness studies or cost-effectiveness appraisals. The MDA's role cannot be compared directly with that of the Medicines Control Agency (MCA), responsible for licensing drugs, as its assessment processes are less structured and its coverage is not comprehensive.

The MDA also has a role similar to the CSM (Committee on Safety of Medicines) in that the MDA is also responsible for the investigation of device-related adverse incidents reported to it by users or by manufacturers. Such investigations may lead to the issuing of advice to the Health Service in the form of Safety or Hazard Notices, or in some cases even modification or recall of the product in question.

MDA has close contacts with both SERNIP and MCIG (Managing Clinical Innovations Group) that supports NICE.

APPENDIX C Implications for Clinical Governance

Clinical Governance in the NHS has been implemented in response to the concerns raised by the problems in Bristol in respect of paediatric cardiac surgery. These problems related to the delivery of well established interventions. These interventions had been the subject of data collection for audit purposes as part of a national cardiothoracic audit programme, which permitted valid comparisons to be made.

The introduction of new procedures in any Trust has, at least until the advent of SERNIP, been subject to no systematic mechanisms. Yet the risks to patients (and the Trust) may be substantial. In addition, the ethical issues are more extreme than for standard research. In particular, informed consent is problematic in the absence (certainly at the start) of information and when the choices available to patients are stark. Because of the small numbers of patients likely to be subject to any such intervention in any one Trust, it is unlikely that valid information can accrue from even a well constructed dataset.

Local experience indicates the existence of only ad hoc processes which may involve an ethics committee (research or other) or simply a discussion with the Medical Director.

It is recommended that:

1. **Trusts** establish more structured processes for the consideration and introduction of experimental procedures including:

    1.1 Referral for consideration by an ethics committee, constituted appropriately to discuss the issues (e.g. high proportion of lay representation, given the likely paucity of medical information);
    1.2 Registration with SERNIP;
    1.3 Resource allocation for systematic data collection.

2. The **NHS R&D Directorate and/or Academy of Medical Royal Colleges** draw up explicit guidelines on the introduction of experimental procedures, with particular reference to patient consent issues and registration with SERNIP, and establish the relevance to Clinical Governance.

3. These responses must address carefully the delicate balance between the rights of individual patients and the need to encourage innovation.

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