



UNIVERSITY OF  
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A Comparison of Fenestrated  
Endovascular Aneurysm Repair (fEVAR)  
with Alternative Treatment Strategies  
(Volume 1)

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By

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## Abbreviations

- AAA – Abdominal Aortic Aneurysm
- ACE - Aneurysme de l'aorte abdominale:Chirurgie versus Endoprothese
- ASA - American Society of Anesthesiologists
- AXR – Plain Abdominal Radiograph
- BMI – Body Mass index
- BSET - British Society for Endovascular Therapy
- CA – Coeliac Axis
- CEUS – Contrast-Enhanced Ultrasound
- CLL - Centre Lumen Line
- COPD – Chronic Obstructive Pulmonary Disease
- CT – Computed Tomography
- CTA - Computed Tomography Angiography
- CVA - Cerebrovascular Accident
- DM – Diabetes Mellitus
- DREAM - Dutch Randomized Endovascular Aneurysm Repair
- DSE - Dobutamine Stress Echocardiogram
- DUS – Duplex Ultrasound
- ECM - Extracellular Matrix
- eGFR – Estimated Glomerular Filtration Rate
- EIA - External Iliac Artery
- EUROSTAR - European Collaborators on Stent-graft Techniques for Aortic Aneurysm Repair
- EVAR - Endovascular Aneurysm Repair
- fEVAR – Fenestrated Endovascular Aneurysm Repair

- GI - Gastrointestinal
- GLOBALSTAR - Global Collaborators on Advanced Stent-Graft Techniques for Aneurysm Repair
- HIT - Heparin Induced Thrombocytopenia
- I+D - Incision and Drainage
- IFU - Indications For Use
- IHD – Ischaemic Heart Disease
- IIA - Internal Iliac Artery
- IMA - Inferior Mesenteric Artery
- IQR – Interquartile Range
- LRA – Left Renal Artery
- MI – Myocardial Infarction
- MIBI - Myocardial perfusion scan (using Methoxy-Isobutyl-Isonitrile)
- MMP – Matrix Metalloproteases
- MUGA - Multi-gated Acquisition scan
- NVR – National Vascular Registry
- OR – Open Repair
- OVER - Open Versus Endovascular Repair
- PTA – Percutaneous Transluminal Angioplasty
- PVD – Peripheral Vascular Disease
- RCT - Randomised Controlled Trial
- RLUH – Royal Liverpool University Hospital
- RRA – Right Renal Artery
- SMA – Superior Mesenteric Artery
- TIA - Transient Ischaemic Attack

- TV – Target Vessel
- UK – United Kingdom
- UKSAT - UK Small Aneurysm Trial
- USA – United States of America
- USS - Ultrasound Scan
- vPOSSUM – Vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity

## **Abstract**

### **Introduction**

Fenestrated Endovascular Aneurysm Repair (fEVAR) is one of a multitude of treatment options for repairing a juxtarenal aortic aneurysm. Alternative treatment options include open repair using a prosthetic graft and endovascular repair using a standard EVAR device outside the intended manufacturer's indications for use (IFU). Although there is perceived benefit of fEVAR over open repair and assumed deleterious effects of using standard EVAR outside of IFU, it is not known which of these three treatment options would result in the best clinical outcome when treating an aneurysm that would be anatomically outside the IFU for standard EVAR. For simplicity, this type of aneurysm is referred to as a non-standard aneurysm.

The hypothesis tested in this thesis is that fEVAR has the best clinical outcome as a treatment strategy for non-standard abdominal aortic aneurysms (AAAs) that are unruptured in whom aneurysm repair is deemed to be more beneficial than conservative management. "Best clinical outcome" relates to the clinical outcome measures: all-cause mortality, aneurysm related mortality and clinical success as defined by agreed reporting standards throughout all follow up time points. The outcome measures regarding mortality will be weighted equally to each other and clinical success will be weighted less than those pertaining to mortality.

### **Method**

To test the hypothesis a retrospective concurrent cohort study was carried out assessing the clinical outcomes of three categories of patients: those treated by traditional open operation, fEVAR, and a standard EVAR performed outside of IFU for non-standard aneurysms. A non-standard aneurysm is defined as one that falls outside the instructions

for use for standard EVAR in relation to anatomical features of the aortic neck. Analysis of all patients who underwent aneurysm repair for a 'non-standard aneurysm' in the Cheshire and Merseyside region in the 24-month period 1<sup>st</sup> April 2006 – 31<sup>st</sup> March 2008 were to form the basis of data for this study. The preoperative computed tomography (CT) scan of each patient was scrutinised separately by two observers to assess if they met the inclusion criteria i.e. if the aneurysm was outside the IFU for standard EVAR. Patients were excluded from analysis if they had a previous surgical or endovascular repair of their aneurysm or if they exhibited an aneurysm that was anatomically within IFU.

Hospital records were then scrutinised to obtain clinical outcome data for each patient according to a proforma. The primary outcome measures included: 30-day mortality/In-hospital mortality, mid-term mortality and aneurysm related mortality, clinical success and technical success.

## Results

80 patients were included in the final analysis from two centres performing aneurysm repair in the Cheshire and Merseyside region. 28 patients underwent treatment with standard EVAR (EVAR), 15 with fenestrated EVAR (fEVAR) and 37 patients underwent AAA repair as an open procedure (OR). The median follow up for all patients was 10.7 years. The results of the primary outcome measures are as follows for EVAR, fEVAR and OR, respectively: In hospital mortality, 7.1%, 0%, and 5.4% – no significant difference. Overall survival at 5 years was ; 54%, 57% and 68% - no significant difference. For the whole cohort (22) 29% of patients survived to 10 years and were alive at the end of the study period. Aneurysm related mortality over length of follow up; 10.7%, 0%, 8.1% - no significant difference. Technical success; 75%, 87% and 97% -  $p < 0.001$ . Clinical failure over the course of the entire follow up was; 46%, 7% and 8% -  $p < 0.001$ . None of the secondary outcome measures.

## Conclusion

Patients who underwent standard EVAR had a significantly worse outcome after their aneurysm repair, attributable to technical success and clinical failure rates. It can therefore be recommended from this study that where possible placement of standard EVAR devices out with IFU should be avoided in preference for an advanced stent-graft technique or open repair. However, it is not possible to accept the hypothesis of this study that fEVAR provides the best clinical outcomes. Further study needs to ascertain the magnitude of any differences in clinical outcomes between OR and fEVAR.

## CHAPTER 1 – Abdominal Aortic Aneurysm

### 1.1. Aneurysm

An aneurysm is defined as a localised dilatation of the wall of a part of the circulatory system. This may include arteries or veins. Aneurysms develop within the arterial circulation more commonly than in either the venous circulation. Arterial aneurysms can be classified according to their type, morphology or location.

#### 1.1.1. Type

Aneurysms can be classed as either true or false aneurysms. True aneurysms involve a dilatation of all three layers of the arterial wall (intima, media and adventitia) whereas false aneurysms do not (See figure 1.1).

*Figure 1.1 Diagrammatic Representation of True and False Aneurysms*

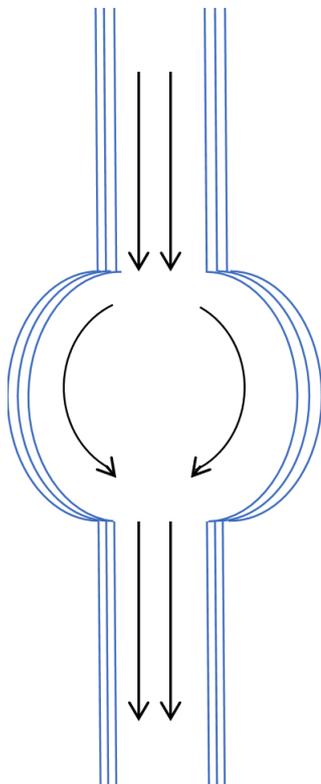


Figure 1a – True aneurysm

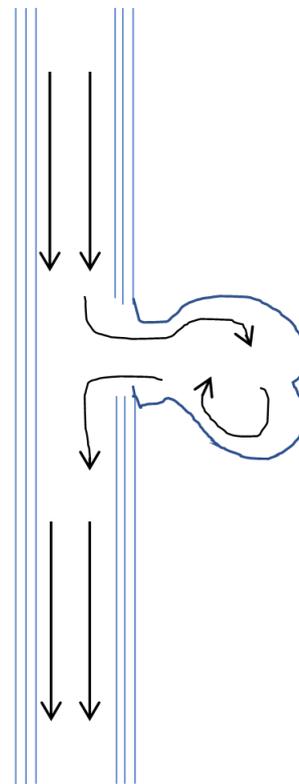


Figure 1b – False Aneurysm

### **1.1.2. Morphology**

Aneurysms can be termed either saccular, sac like projections from the main arterial conduit, or fusiform, spindle shaped. By definition, fusiform aneurysms are thickest in the middle and taper towards each end.

### **1.1.3. Location**

Aneurysms can occur anywhere within the arterial tree, however, the commonest sites for their development are within the aorta, cerebral vessels and popliteal arteries. The most common form of cerebral aneurysm is a saccular aneurysm within the Circle of Willis. These are almost always due to a congenital weakening of the wall of the artery causing the aneurysm. Aortic and popliteal aneurysms, however, tend to be atherosclerotic in nature and are most commonly fusiform in shape. The aorta is the most common site for aneurysm development. Aortic aneurysms can develop within the aortic root, within the thoracic segment of the aorta, within the abdominal component of the artery (abdominal aortic aneurysm, AAA) or as thoracoabdominal aneurysms where the aneurysmal segment of aorta involves both intrathoracic and abdominal components of the artery. The most common site of aneurysm development in the aorta is within the abdominal aorta.

When an aneurysm develops within the abdominal aorta it does so most commonly inferior to the renal arteries, termed an infrarenal AAA. However, an aneurysm can come close to, abut or even extend around and above the renal arteries and in this scenario the aneurysm would be termed a juxtarenal, pararenal or suprarenal aneurysm respectively.

## **1.2. Abdominal Aortic Aneurysm (AAA)**

When a true aneurysm develops within the abdominal aorta it tends to enlarge over time. The majority remain asymptomatic. The problems that can arise from aneurysm enlargement include: pressure on surrounding structures which can result in pain, embolization of thrombus from within the aneurysm to the distal arterial tree, and the

most significant complication – rupture. Once an aneurysm ruptures it commonly results in rapid exsanguination and death. This fact has led to the desire for an adequate and efficacious prophylactic treatment of aneurysms before their rupture and driven further understanding of the disease and its treatment options.

### **1.2.1. Epidemiology**

The incidence and prevalence of aortic aneurysms increase with age. In 2010 the global prevalence rate was approximately 2200 per 100,000 people and the incidence was 165 per 100,000 people in those aged 75 – 79 years. [1] According to the Office for National Statistics there were 5886 deaths secondary to aortic aneurysm or dissection within England and Wales during 2013 making it the 15<sup>th</sup> leading cause of death that year.

Male sex, age, hypertension, hyperlipidaemia, family history and smoking are all risk factors for the development of aortic aneurysms. Furthermore, patients with certain connective tissue disorders are more prone to developing aneurysms such as Marfan syndrome and Ehlers-Danlos syndrome. Cigarette smoking is associated with a five-fold increase for the presence of AAA and as such is felt to be the most important modifiable risk factor related to AAA development and progression. [2]

### **1.2.2. Pathology**

The pathological processes involved in aneurysmal formation and progression are complex and incompletely understood. Transmural vascular inflammatory processes, extracellular matrix (ECM) degradation, and an imbalance in smooth muscle cell haemostasis are all thought to play a significant role in AAA development.[3] Traditionally AAA have been classified as either inflammatory or atherosclerotic however this delineation is somewhat misleading. Although a high proportion of patients with AAA exhibit atherosclerosis, atherosclerosis within the aorta is frequently seen without AAA development. Some aneurysms are described clinically as ‘inflammatory’ exhibiting a classic triad of thickened

aneurysmal wall, extensive perianeurysmal and retroperitoneal fibrosis and dense adhesions of adjacent abdominal organs as described by Walker et al in 1972[4]. However some investigators believe that there is no such clear distinction between 'atherosclerotic' and 'inflammatory' aneurysms and, pathologically, inflammation plays the key role in AAA development meaning that they are the same disease but differing only in their degree of inflammation. [5]

Transmural vascular inflammatory processes seem to be mediated by a myriad of different cells such as neutrophils, T cells, B cells, macrophages, mast cells, NK cells. These infiltrating cells secrete various inflammatory factors including cytokines, chemokines, leukotrienes, reactive oxygen species and immunoglobulins. [3] This inflammatory responses promotes extracellular matrix degradation and as AAA progress an increase in activity of matrix metalloproteases (MMPs), as well as serine and cysteine proteases seem to augment this degradation.[6]

More recently there has been increasing interest in the role genetic factors play in the development of the disease and a study considering AAA prevalence in monozygotic and dizygotic twins suggests a significant genetic contribution to AAA development. [7]

### **1.2.3. Natural History**

Once AAA develops often the natural course is that it will continue to enlarge and eventually rupture resulting in high rates of mortality. The rate of enlargement is not constant and methods of predicting rupture are limited. The most widely used parameter to predict rupture rate is maximum aneurysm diameter as this is both easy to perform using simple imaging techniques (ultrasound scanning) and simple to understand, both for patient and physician. The rate of enlargement of AAA is not linear and Lederle et al found that larger initial aneurysm diameter is associated with an increased rate of expansion suggesting that as an aneurysm grows its rate of expansion also grows. The median rate of

aneurysm diameter increase was 0.32cm per year (IQR: 0.16 – 0.42 cm per year) in that study. [8] As well as the baseline aortic diameter at diagnosis, cigarette smoking appears to cause greater expansion of the aneurysm. Other studies have suggested that reduced forced expiratory volume in one second (FEV1) and hypertension promote quicker aneurysm expansion as well. Although aneurysms are less common in women they tend to expand more rapidly, rupture more frequently and rupture at smaller diameters than in men. It appears that the coexistence of diabetes mellitus and peripheral arterial disease limit the rate of expansion of AAA but the reasons for this are unclear.

The reported rupture rates per year for given maximum aneurysm diameters are: <1% for AAA of 4 – 5.4cm, 9% for AAA of 5.5 – 5.9cm, 10% for AAA of 6 – 6.9cm, 32.5% for AAA >7cm. [8, 9] Randomised controlled trials corroborated these figures for patients with small aneurysms (<5.5cm) confirming that the risk of rupture remains low when the aneurysm is small. Furthermore, these trials showed no benefit in performing intervention on these patients compared to continued surveillance until they were 5.5cm. These findings suggest a rather benign natural history in the main for small aneurysms. Patients who do suffer a ruptured aneurysm have a high mortality rate at approximately 80%. Those that undergo surgical repair of a ruptured aneurysm having in-hospital mortality rate of approximately 50%. [10]

It is also important to note that the incidence of AAA and that of ruptured AAA is declining over time, although the reasons for this are not entirely understood it appears to be following the trend with a reduction in smoking prevalence in the adult population.

The natural history for aneurysms >5.5cm is less well-known because this is the threshold for consideration of surgical repair and as such there are limited studies evaluating what happens to patients above this size. In one study for patients deemed unsuitable for AAA repair the following data was reported:

- 5.1 – 6.0cm AAA – Median survival 44 months, 11% died of rupture
- 6.1 – 7.0cm AAA – Median survival 26 months, 20% died of rupture
- >7cm AAA – Median survival 6 months, 43% died of rupture

However, in those 72 patients, with AAA ranging from 5.3 to 12cm, 60% were alive at the end of the study period (2 years). The median survival for the cohort was 34 months and the 5-year survival was 4.2%.

Noronen et al (The natural course of abdominal aortic aneurysms that Meet, 2013) also investigated the fate of patients deemed unsuitable for aneurysm repair. With a median follow up of 19 months after decision not to operate 36.4 % of patients had ruptured. The following data is from that study:

- 5.5 – 6.0cm AAA – Median survival 24 months, 42% died of rupture
- 6.1 – 7.0cm AAA – Median survival 14 months, 44% died of rupture
- >7cm AAA – Median survival 11 months, 44% died of rupture

For the whole cohort the median survival time was 14.8 months and 22.1% were alive at the end of follow up.

The UK Endovascular Aneurysm Repair 2 (EVAR 2) trial randomised patients to either receive endovascular repair or no repair in patients considered unsuitable for open repair. In the cohort randomised to no intervention 9.2% had died after 6 months, 61% after 4 years and only 8.5% were alive at 12 years. The mean survival was 4.2 years for the whole study population and was not different between the intervention and no intervention groups.

These studies of course document the experience of patients who are considered unfit or turned down for aneurysm repair for one reason or another and the true natural history of any given aneurysm cannot be definitively stated from these studies. However, they

provide the only limited insight available to the natural history of aneurysm greater than 5.5cm. What is clear is that in these comorbid and often elderly patients their risk of short-term mortality from their aneurysm as well as other causes remains high. The overall mortality for the population of patients deemed suitable for operative intervention may be lower than seen in the above studies if they were not to undergo aneurysm repair. However, it is reasonable to suggest that their aneurysm related mortality, although may still be lower, would be similar and if this is the case then this would continue to support the rationale for operating on patients when their aneurysm reaches 5.5cm or other predefined criteria such as rapid expansion. The paucity of data for the natural history of abdominal aortic aneurysms also means that there is no information within the literature specifically about the natural history of different types of abdominal aortic aneurysm and whether infrarenal, juxtarenal or suprarenal aneurysms behave differently from each other.

#### **1.2.4. Screening**

Due to the high mortality of ruptured AAA there has been an argument for population screening in order to detect aneurysms before they rupture. The aim of screening is therefore to detect more aneurysms when they could feasibly be directed for elective treatment to reduce the mortality within the population from this disease. Several countries now have population screening for AAA underway including Sweden, U.S.A., and the United Kingdom. There have been four large randomised controlled trials (RCT) of population screening for AAA [11-14] and in 2007 a Cochrane meta-analysis of the four trials was conducted which revealed that for men between the ages of 65 – 79, an invitation to screening reduced the aneurysm related mortality by 40% at 3 – 5 years of follow up. A significant decrease in incidence of ruptured AAA was also seen in the group invited for screening. [15] Only one of the four trials included women and failed to show any benefit in terms of aneurysm related mortality for those screened. However, the

prevalence of AAA in women is much lower than that for men and there is therefore a lack of evidence to identify whether women should also be invited for screening or not. There is some evidence that suggests selective population screening for women, for example those that are current smokers, may be cost-effective and yield benefit [16] however there is currently no population based screening programme that includes women.

## CHAPTER 2 – Management of AAA

### 2.1. Introduction

The primary aim in the management of AAA is to prevent death secondary to aneurysm rupture. The most important factor that predicts aneurysm rupture and therefore mortality for any patient with a given AAA size is the maximum diameter of the aneurysm. [17-19] Elective surgical repair of an abdominal aortic aneurysm is the most effective means of preventing rupture. There has, as yet, been no pharmacological agent found that halts progression or causes regression of abdominal aortic aneurysm once formed. Operative management carries an inherent mortality risk and the decision whether to treat an aneurysm with an operation should be based on the clinical judgement pre-operatively of whether the risk of death from operation is less than that if the aneurysm is not operated on. Historically there was debate at what size of aneurysm patients should undergo elective surgery, some authors would argue that all aneurysms once detected should be considered for elective repair of their aneurysm. However through the 1980's and early 1990's evidence began to accumulate that those patients with small aneurysms (<5cm) had a low risk of rupture in the intervening years and therefore should be offered close surveillance and monitoring of the size of their aneurysm with ultrasound. [18] The UK Small Aneurysm Trial (UKSAT) sought to answer the question by means of a randomised controlled trial whether those patients with an aneurysm of 4.5 - 5.5cm were better served by 'early operation' or continued surveillance and found that there was no survival benefit over the longer term for those patients operated on early. [20] Therefore the figure of 5.5cm maximum aneurysm diameter is used as the 'threshold' for when elective surgical repair should be considered. If an aneurysm is detected and is less than 5.5cm patients will often be treated conservatively and enter a surveillance programme with regular ultrasonography examinations to monitor the expansion of their aneurysm. [8] These

findings support the decision to observe aneurysms that are less than 5.5cms in size, this includes whether an aneurysm is operated on by endovascular means also. [21, 22]

Once an unruptured aneurysm has been identified and if it is considered large enough to merit surgical repair the patient will be assessed and counselled regarding repair of their aneurysm. If the patient and physician decide to proceed with surgical repair of the aneurysm, then there are broadly two methods of repair available: open surgical repair or endovascular placement of a stent-graft. In all cases of repair the primary aim is to reduce the risk of death from aneurysm rupture at a later date by excluding the aneurysm from the circulation. Important in this decision making is the relative rupture risk of any given aneurysm and the risk of operative intervention, in whatever form, for any given patient.

## **2.2. Rupture Risk of AAA**

As already stated, the aim in management of AAA is to prevent rupture and although baseline aortic diameter has the greatest role in predicting rupture of AAA there are other factors that may affect the natural history or rupture risk in an individual patient. Therefore, the diameter of 5.5cm as a threshold for operative management of AAA should not be absolute and the decision to operate or not should be based on multiple factors.

As stated before aneurysm expansion occurs at a relatively predictable rate overall but individual aneurysms can expand at different rates. It has also been shown that larger aneurysms tend to expand at a faster rate meaning that their risk of rupture is not only higher to begin with but continues to increase more quickly than either a smaller aneurysm expanding at the same rate or a large aneurysm that is not expanding at all.[23] Rapid expansion of an aneurysm, defined as >5mm within six months or >10mm within one year, has also been determined to be an indication to undergo elective aneurysm repair. [24] It is difficult to ascertain whether expansion itself is a predictor of aneurysm rupture

independent of aneurysm diameter but theoretically a rapidly expanding aneurysm may represent instability of the aortic wall and be a sign of impending rupture.

Cigarette smoking is associated with the expansion of AAA and an increased risk of rupture. [25-27] Smoking cessation therapy is also associated with a reduction in the need for aneurysm repair and eventual rupture. [28] A metaanalysis of over 15,000 patients across 18 studies found that smoking increased the growth rate of aneurysms by 0.35mm/year and rupture rates were twice that of non-smokers. [29]

Although hypertension is often quoted as a significant risk factor for AAA growth the literature fails to consistently show a strong association between hypertension and aneurysm expansion. [25, 27, 30] From the ADAM study there was a positive statistically significant association between increase in diastolic blood pressure and AAA expansion rate correlating to 0.2mm/year increase per 10mmHg increase in diastolic blood pressure. [25] However in the UK small aneurysm trial there was no statistically significant association between blood pressure and aneurysm growth. [27] That study did however find that after 3 years follow up there was an increased risk of rupture with increasing blood pressure. [30]

Respiratory disease, primarily COPD, with an associated decrease in the forced expiratory volume in one second (FEV1), appears to be associated with an increased risk of aneurysm rupture. [30]

The prevalence of AAA in women is lower than men but in women that do have an aneurysm multiple studies have shown that their aneurysms tend to grow faster, rupture more frequently and rupture at smaller AAA diameters. [30-32] This is true even when controlling for other factors known to influence rupture risk. Therefore, the presence of an

abdominal aortic aneurysm seems to be a more aggressive and lethal disease when it is present in a woman.

Baseline maximum aneurysm diameter remains the most influential factor in predicting both aneurysm expansion and rupture risk, but rate of aneurysm expansion, tobacco use, hypertension, respiratory disease and female sex also play an important adjunctive role in determining rupture risk. Therefore, when assessing a patient to determine the most appropriate treatment option all these factors should be taken into consideration when trying to predict their risk of aneurysm rupture. There may also be a rationale given certain characteristics for determining that the threshold for aneurysm repair may be lowered or even raised for an individual patient. For example, a female patient who is a smoker may have a greater rupture risk for a 5cm aneurysm than a male non-smoker with a 5.5cm aneurysm. It would therefore be sensible to consider repair of her aneurysm at this 'sub threshold' size given these characteristics. This argument takes into consideration the small numbers of women enrolled into the major randomised controlled trials that overall showed no benefit for patients undergoing repair when their aneurysm is less than 5.5cm.

### **2.3. Medical Management of AAA**

All patients with a diagnosis of abdominal aortic aneurysm should be referred to a vascular service where a decision about initial management strategy can be made. Important in this consultation is also the explanation to the patient of what an aneurysm is, its natural history and therefore the importance of surveillance (for small aneurysms) and ensuring the initiation of appropriate medical management. All patients diagnosed with an aneurysm should have the same care and attention to appropriate medical, non-operative, management regardless of aneurysm size.

Smoking cessation therapy is an important part of the medical management for any smoker with an aneurysm. As stated above smokers have a higher rate of expansion and rupture.

One study that assessed the cost effectiveness of an intensive smoking cessation programme found that the intervention (8 week smoking cessation programme, adjuvant pharmacotherapy and annual revisits) was cost effective by reducing the need for AAA repair and rupture over a 10 year follow up. [28] Furthermore it has been shown that patients surgery who stop smoking have fewer post-operative pulmonary complications [33]. Active smoking cessation therapy should therefore be part of the treatment of anyone with an abdominal aortic aneurysm who smokes.

There have been numerous animal and in vitro studies that have suggested possible pharmacological targets to inhibit AAA progression however, as yet, there are no agents that have been found to consistently prevent AAA expansion or rupture. A large multicentre study of 5362 patients found no association between commonly used cardiovascular mediations (statins, beta blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and AAA progression. [34]

In a randomised controlled trial assessing the effect of beta blocker versus placebo no overall difference was seen in the expansion rate of small AAA with no significant difference in the proportion of patients undergoing elective surgery. [35] In that study propranolol was the beta blocker of choice and was poorly tolerated with 42% of the 276 patients randomised to receive propranolol stopping their medication early because of side effects. Interestingly when the authors analysed the results for those patients still taking propranolol, they found that fewer patients underwent aneurysm repair compared with placebo and although growth rates were not statistically different there were fewer people who had rapid expansion of their AAA. These results of course do not confirm that beta blockade is beneficial for patients with a small aneurysm but there is an important area for future research to see if a better tolerated beta blocker does provide some benefit.

Regarding ACE inhibitors and ARBs – there have been conflicting reports from studies in the literature to date about the role of these medications on aneurysm expansion. One large scale study that retrospectively evaluated prehospital use of ACE inhibitors found that patients taking ACE inhibitors were less likely to present with a ruptured aneurysm than those who weren't taking them. [36] However the UK small aneurysm study found an increased risk of aneurysm expansion in those taking ACE inhibitors. [37] One randomised controlled trial that assigned patients to an ACE inhibitor, amlodipine or placebo found no difference in annual growth rates or in the proportion of those undergoing repair. [38] Therefore there is insufficient evidence to suggest that these agents provide any benefit for patients with small AAA.

Statins have a theoretical impact on AAA development related to their known effect on the expression of MMPs. MMPs are thought to play a role in the degeneration of the arterial wall leading to the development of and progression of AAA.[39, 40] Some animal studies have suggested that statin therapy may slow progression of AAA as well. [39, 41-43] A meta-analysis comparing results of 11933 patients across 12 studies found that statin therapy had no significant effect on AAA expansion rate but did show a post-operative mortality benefit. [44] This highlights what is probably the most important feature of statins - their protective cardiovascular effect from sequelae of atherosclerosis. Therefore, there is limited evidence that statins may limit the progression of AAA, but they provide a long-term survival benefit in those undergoing AAA repair and are generally a well-tolerated medication. On this basis all patients with AAA and without contraindication should be prescribed statin.

Antiplatelet therapy has not been convincingly shown to limit the rate of AAA expansion in multiple studies but like statin there are well documented protective effects of antiplatelet therapy in patients with cardiovascular disease.[37, 45, 46] Due to the strong association of

AAA with cerebrovascular atherosclerosis it is reasonable to treat these patients with antiplatelet medication to further modify their cardiovascular risk. Furthermore, a large study in the UK investigating the effect of statins, antiplatelet therapy and antihypertensive agents evaluated records of 12485 patients with a known diagnosis of AAA. This study showed that between 2000 and 2012 the proportion of patients receiving these medications increased and also demonstrated 5 year survival improved for patients taking these medications compared to those who did not.[47]

Antibiotics have also been investigated for their role in limiting expansion of AAA. This was because there was an initial suggestion that infection may play a role in AAA formation as a study found that presence of *Chlamydiae pneumoniae* infection was associated with AAA expansion. [48] Further studies showed that antibiotics may limit AAA expansion rates there is no clear evidence that antimicrobial action provides benefit for the majority of AAA that are non-infected. [49] Tetracycline antibiotics are also known to inhibit MMPs and therefore their role in modifying aneurysm expansion has been investigated. To date no study has definitively shown that the use of tetracycline antibiotics affects the progression of AAA. [50, 51]

In summary, although multiple agents have been investigated there are none that can halt or cause regression of an aneurysm once formed. There is some suggestion that beta blockers and statins may modify AAA progression, but further study is needed to determine the true effect of these agents. All patients with a diagnosis of AAA should have active smoking cessation therapy, antiplatelet and statin therapy if there are no contraindications. Hypertension has been shown to increase rupture risk and it therefore seems sensible to advocate aggressive management of hypertension but there is no evidence to suggest one antihypertensive agent is better than any other for patients with small AAA.

This management strategy is also aimed at controlling associated risk factors and limiting their impact on the health of the patient. This is to improve the overall health of the patient and should the patient need an operation in the future they will benefit from having these conditions optimally medically managed before intervention for their aneurysm. Surveillance with regular ultrasound examination to monitor and document the size of their aneurysm should also be considered an important part of this management strategy as it will identify the point, if the patient does not die from another cause first, at which they should be considered for operative intervention in a timely manner which therefore will reduce the risk of aneurysm rupture. Of course, it may be decided that an aneurysm should not be surgically repaired and therefore patients may be “turned down” for aneurysm repair. The decision-making process will be individual for each patient but an assessment of risk versus benefit would be made and a patient may be turned down for aneurysm repair before it ruptures for elective repair, but still be considered for emergent repair or turned down altogether.

### **2.3.1. Turndown for Repair**

There is a paucity of data recording the proportion of aneurysms that are turned down for operative intervention however a few studies have documented turndown rates between 13% - 37%.<sup>[52-55]</sup> The most oft quoted reason for patients being turned down in these studies is the existence of significant medical comorbidity. Other reasons include anatomic unsuitability, and patient choice. The median survival for these cohorts of patients after decision not to operate ranged from 15 – 34 months. In all the studies less than 50% of the patients suffered a ruptured aneurysm highlighting the severe nature of comorbidities in this patient population. There were varying methods by which patients were investigated and risk stratified to determine whether to operate or not but in most of the studies no validated aneurysm risk scoring model was used. This suggests two things: given the high rate of early death from non-aneurysm related causes there is significant utility in the

clinical assessment of a patient to determine their likely outcome. Secondly with nearly a third of patients dying from rupture in most series the question remains about whether a proportion of these patients would have been better suited with aneurysm repair and how best to define and identify those patients.

If it is decided that an aneurysm should be repaired then this can be done, broadly speaking, by two methods; open surgical repair or endovascular repair. These treatment strategies are detailed below.

#### **2.4. Open Surgical Repair of AAA**

The first successful surgical resection of an abdominal aortic aneurysm was performed by Dubost in Paris, 1951. [56] The aneurysm was replaced with cadaveric aortic homograft to restore circulation distally. Although modern techniques of open surgical repair utilise prosthetic material for arterial grafts the principles of the operation remain the same.

Under general anaesthetic the abdominal aorta within the retroperitoneal space is accessed usually through laparotomy and the transperitoneal route, however as Dubost did, it can be accessed retroperitoneally via a thoracoabdominal incision on the flank. Once access is gained the aorta is clamped proximal and distal to the aneurysm (usually on the iliac vessels) to enable access to the lumen of the aorta without exsanguination. The aneurysm is incised and thrombus from within the aneurysm is removed. Any back-bleeding vessels from within the aneurysm are suture ligated at this point including the inferior mesenteric artery, if necessary. A prosthetic surgical graft (which can be tubular or bifurcated as needed) is sutured to the rim of aortic tissue immediately proximal to the aneurysm, usually below the renal arteries. The distal portion is then sutured to either the distal aorta or iliac vessels. The clamps are removed and the circulation to the peripheries is restored. The aneurysm sac is sutured over the prosthetic graft to minimise risk of adhesions and aortoenteric fistula.

#### **2.4.1. Complications of Open Surgical Repair of AAA**

The most devastating complication after aneurysm repair is death. Open surgical repair is a major intervention, due to the nature and epidemiology of the disease it is usually performed in elderly people with many co-existing medical conditions. This translates into a high immediate and peri-operative mortality rate for these patients. The estimated 30-day mortality rate for patients undergoing elective open surgical repair of an infrarenal AAA is 4.7% [57].

There have been many models developed to estimate which patients are at a higher risk of mortality after elective aneurysm repair and as such there have been many factors found to be associated with an increased risk of mortality. A study by Grant et al. [58] which assessed and compared five such risk prediction models found that in the two best performing models there were common characteristics associated with an increased risk of peri-operative mortality and these were: increasing age, female sex, renal disease and vascular disease. In addition, respiratory disease and cardiac disease were associated with higher mortality rates separately between the two models.

#### **2.4.2. Morbidity of Open Surgical Repair of AAA**

Open surgical repair is a significant intervention and therefore there is significant risk of complication after the operation. Complications can be either local (such as wound infection, atheroembolism, bleeding, graft infection, anastomotic pseudoaneurysm) or systemic (such as stroke, myocardial infarction, and renal failure) these complications can result in death, limb loss and/or long-term reduction in independence and quality of life. The reported rates, in a meta-analysis, of significant systemic complications after open repair in the post-operative period are as follows: Stroke (1.9%), Myocardial Infarction (9.2%), Renal Failure (10.4%). [57]

Late complications after open repair appear to be relatively rare with reported rates of long-term complications being low, such as anastomotic pseudoaneurysm (3%), graft thrombosis (2%) and aorto-enteric fistula (1.6%). These complications were observed to be a median of 4 – 6 years after initial repair. [59] Therefore with open surgical repair the most significant risk is loaded at the beginning meaning if patients survive their initial operation and post-operative period without a significant complication, they are generally free from complication or re-intervention after that.

## **2.5. Endovascular Repair of AAA**

In endovascular aneurysm repair (EVAR) the risk of aneurysm rupture is attenuated by excluding the aneurysm from the circulation by means of placing a metallic stent covered with fabric (a stent-graft) across the aneurysm from within the circulation. Under general, regional or local anaesthetic access to the circulation is gained via the femoral arteries. A stent-graft is then inserted under fluoroscopic guidance to the aneurysm. Once deployed the metallic stent acts to provide radial force and fixation to the arteries above and below an aneurysm with the fabric preventing blood entering the aneurysm itself. By removing the aneurysm from the circulation in this way the aneurysm is no longer subject to the haemodynamic forces of the circulation and its risk of rupture decreases. Furthermore, if the aneurysm does rupture but is still excluded from the circulation then the rapid exsanguination and death seen from rupture in untreated aneurysms would not occur. The operation is completed by repair of the femoral arteries that acted as access sites. Juan Parodi and colleagues are credited with the first successful use of such a stent-graft to successfully achieve aneurysm exclusion in a patient in 1990. [60]

The perceived advantage of this technique is that it removes the need for direct access to the aneurysm itself through a laparotomy or thoracoabdominal approach thereby limiting the surgical insult that occurs. Initially this advantage was used in patients who exhibited a

particularly high risk of death or complication from standard open surgical repair. Over time, however, the techniques and devices used have been refined and in fact it is the most common method of infrarenal aneurysm repair used today. EVAR accounted for 74% of the total number of AAA repairs performed in the United States in 2010 [61].

### **2.5.1. Special Considerations for Endovascular Repair – Fixation**

One of the key differences between open aneurysm repair and endovascular repair is the method by which the graft or stent-graft is fixed in place within the aorta. In open repair the graft is hand sutured by the surgeon to a circumferential ring of aortic tissue proximal to the aneurysm. In endovascular repair the stent-graft is placed within the lumen of the aorta from below (while its diameter is constrained within a delivery system). Once at the appropriate level it is expanded to a larger diameter. This happens as the delivery system is withdrawn, unsheathing the device itself. The majority of the expansion to a larger diameter is due to the self-expanding nature of the stent-graft which is intentionally manufactured this way but can also be aided by expanding an endovascular balloon within the lumen of the stent-graft to ‘push’ out the device. As such, there is no direct suturing of the stent-graft to the aorta. It relies on the radial force of the proximal stent-graft as well as additional components such as hooks and barbs (that ‘bite’ into the aortic tissue and engage with it) to provide ‘fixation’ of the device to the aortic wall so that it doesn’t move caudally, also known as migration.

This fact means that open repair grafts do not migrate caudally due to the secure fixation whereas it is possible that a stent-graft may. Migration can lead to inadequate ‘seal’ at the proximal end of the stent-graft allowing blood to once again flow into the aneurysm exposing the patient to risk of rupture. Migration may also cause kinking of the distal portion of the stent-graft that may lead to disturbances or even cessation of the flow of blood into the iliac arteries. Much work has been done on the fixation forces of various

types of stent-grafts and the 'distraction' forces which they are exposed to using experimental bench top models with animal, human or artificial aortas and mathematical models (such as computational flow dynamics). In an analysis of over 4000 patients who underwent standard EVAR from the EUROSTAR registry it has been shown that patients with shorter and wider infrarenal necks are more likely to experience migration [62], confirming the opinion that the anatomy of an aneurysm, especially at the site of fixation, plays a significant role in outcome after endovascular repair.

### **2.5.2. Special Considerations for Endovascular Repair – Seal**

To exclude the aneurysm from the circulation an endovascular device should be placed in a position to stop blood flow into the aneurysm. As stated above the fixation of the stent-graft to the aorta is from within the lumen and not, as in open repair, a continuous suture around the circumference of the aorta. This means that there is a potential space between the fabric of the stent-graft and the aortic wall where blood could continue to flow into the aneurysm. Due to this, it is imperative that a good 'seal' is achieved above and below the aneurysm. These are termed the proximal and distal seal zones, respectively. To improve the seal between the stent-graft and aorta the device should have adequate radial force so that the fabric is in contact with the aortic wall, and consequently be of an adequate size to expand to the diameter of the aorta. It should also be deployed within a segment of artery that is relatively free from intraluminal disease that could distort the fabric and hence compromise the seal. The 'seal zone' must also be in a relatively straight sided portion of aorta that is long enough to achieve a good seal especially considering the possibility that a stent graft may move or migrate through its lifetime.

The importance for good fixation and seal from an EVAR device has led to the development of specific 'indications for use' recommendations by the manufacturers of stent grafts. Indications for use are recommendations an aneurysm must exhibit for the device to

perform adequately to achieve aneurysm exclusion. Most these recommendations relate to anatomical features that may affect the fixation or seal that a device will deliver.

### 2.5.3. Complications of EVAR

Despite the less invasive nature of EVAR compared with open repair it is still a major intervention and as such there is an appreciable risk of death related to the procedure. The 30-day mortality rate for EVAR reported in the literature is in the region of 1 - 2% [63, 64]. The complications for EVAR include most of those detailed for open surgical repair including local and systemic complications such as MI, stroke and renal failure.

Specific complications to EVAR include; conversion to open repair either immediately or after a period, endoleak and graft migration. The term endoleak was first defined by White and colleagues in 1997[65] as *“...the persistence of blood flow outside the lumen of the endoluminal graft but within an aneurysm sac...being treated by the graft. Endoleak is due to incomplete sealing or exclusion of the aneurysm sac...”*. This phenomenon has been classified according to the site where the ‘leak’; originates from (See table 2.1):

**Table 2.1 Description of Types of Endoleak**

Endoleak	Site of Endoleak
<b>Type I</b>	Failure of seal at the proximal (Ia) or distal (Ib) attachment sites
<b>Type II</b>	Blood flow into the aneurysm from side branch vessels such as lumbar or mesenteric arteries
<b>Type III</b>	Failure of the device causing blood flow into the aneurysm at a modular connection (IIIa) or a tear in the fabric of the device itself (IIIb)
<b>Type IV</b>	Flow through porous fabric (<30 days after device deployment)

Compared with open repair EVAR is more prone to failure at a later stage. Late aneurysm rupture remains a problem that is significantly more common after EVAR compared with open repair. The proportion of patients experiencing late aneurysm rupture, as detailed in

a meta-analysis, were 2% (EVAR) and 0.3% (Open repair) [57] with the vast majority of ruptures after EVAR occurring within the first two years after initial operation. [66] Although late aneurysm rupture represents catastrophic failure of the device in EVAR this may be preceded by several differing modes of failure, such type Ia endoleak, type III endoleak, migration or a distorted endograft. These modes of failure are also risk factors for late conversion to open repair within the same analysis by the EUROSTAR collaborators. [66] Furthermore specific anatomic characteristics such as short neck length and significant neck angulation have been shown to be associated with higher incidences of type Ia endoleak, suggesting that specific anatomic characteristics may predispose to higher failure rates. [67, 68]

#### **2.5.4. Follow up after EVAR**

Due to the risk of late failure, and the fact that a device may exhibit a mode of failure before actual rupture of the aneurysm, it is necessary that patients undergo post-operative surveillance. Surveillance is aimed at trying to detect these modes of failure before they lead to rupture, primarily because there are treatment options that can rectify these failures ranging from conversion to open repair to endovascular methods of correcting endoleaks or improving fixation and seal. Patients can undergo surveillance to detect device failure via ultrasound imaging (To detect aneurysm expansion +/- endoleak), plain abdominal radiography (To detect migration and/or stent fracture) and computed tomography (CT) scanning (which can detect all the above). Patients will generally undergo imaging with a combination of ultrasound and plain abdominal radiography +/- CT scanning at regular intervals for the remainder of their life. Should a failure be detected the patient will be investigated and considered for secondary intervention if appropriate and necessary.

Secondary intervention after EVAR remains relatively common and may be necessary in up to 9% of patients at some point during their follow up. In those that do receive a secondary intervention the majority are performed because of endoleak and are endovascular reinterventions. [69]

## 2.6. Randomised Controlled Trials of EVAR versus Open Repair

To date there have been four randomised controlled trials (RCTs) comparing the clinical outcomes of standard EVAR and open repair (OR) for infrarenal AAA. The table below details the pertinent facts relating to these trials. (See table 2.1)

*Table 2.1 Randomised Controlled Trials Comparing EVAR and OR*

Trial	Years Recruited	EVAR (n)	Open Repair (n)	Mean Follow Up (Years)	In Hospital Mortality (EVAR)	In Hospital Mortality (Open)
UK EVAR Trial 1[70]	1999 - 2004	626	626	6	1.8%	4.3%
DREAM[71]	2000 - 2003	173	178	6.4	1.2%	4.6%
OVER[72]	2002 - 2007	444	437	5.2	0.5%	3%
ACE[73]	2003 - 2008	150	149	3	1.3%	0.6%

Table 2.1 - ACE = Aneurysme de l'aorte abdominale:Chirurgie versus Endoprothese, DREAM = Dutch Randomized Endovascular Aneurysm Repair, OVER = Open Versus Endovascular Repair

The French ACE trial did not find a statistically significant difference in the short-term mortality after operation. This trial specifically investigated those patients whom presented a low or intermediate risk for open operative intervention and differs from the other trials in that respect. The remaining three RCTs showed a significant survival advantage for patients undergoing EVAR in the short term. A review by the Cochrane Collaboration confirmed that when comparing all four RCTs there was a clear benefit in terms of short-term mortality for EVAR (1.4% vs 4.2%,  $p < 0.0001$ )[74].

In all trials the rates of all-cause mortality equalise over the follow up period with no significant difference between EVAR and OR over the longer term in terms of all-cause mortality. The UK EVAR Trial 1 describes the convergence of mortality rates at two years [70]. The DREAM Trial reported convergence of mortality rates at one year after operation.[75] The OVER trial reported a convergence of mortality rates at three years after the operation.[76] With a median follow up of 3 years the ACE trial did not find a difference in all-cause mortality at any follow up point to three years. [73]

Aneurysm related mortality rates show that EVAR confers an early benefit, which in the three trials that did show benefit for EVAR, was due entirely to the early post-operative benefit of EVAR. The early advantage of EVAR in this regard was also lost throughout follow up, with convergence of survival curves. The trial investigators explained this convergence of aneurysm related mortality to be due in part to late endograft failures resulting in aneurysm rupture. [70] Another explanation was that in general “frail” patients who underwent open repair simply died while in hospital whereas those same frail patients who underwent EVAR survived their operation but then died soon after as a consequence of their general health and physiological status. [76]

The review by the Cochrane collaboration found that between the four trials there were no significant differences in terms of the following major complications experienced by EVAR or OR groups: Myocardial complications, stroke, renal dysfunction (using surrogate markers such as creatinine and eGFR levels), and sexual dysfunction. The analysis however did identify a significant difference in terms of pulmonary complications and pulmonary related deaths, with EVAR performing better. [74] The comparison of reinterventions after the initial operation shows that the reintervention rate was significantly higher in the EVAR group (23.4%) compared with OR (13.1%) at long-term follow up. [74]

The most significant non-randomised study found in the literature search is a comparison of propensity matched cohorts of the Medicare population in the U.S.A. undergoing either EVAR or OR between 2001 and 2004. [77] There were 22, 830 matched patients in each cohort analysed. The perioperative mortality rate seen compares with the RCTs, with 1.2% for EVAR and 4.8% for OR. This analysis showed convergence of the survival curves at approximately three years from the initial operation. Reinterventions related to the aneurysm were found to be more common after EVAR in this analysis also (9% vs 1.7%). Interestingly the rates of major post-operative complications were significantly higher in the open repair group; namely myocardial infarction, pneumonia, renal failure, deep vein thrombosis or pulmonary embolism.

Overall the published evidence comparing EVAR and OR is vast but consistently a survival benefit in the short term is seen after EVAR compared with OR. Over the longer term this survival benefit is lost somewhere between 1 and 3 years, with an increased number of deaths after the initial post-operative period in the EVAR group. It is uncertain whether aneurysm related deaths or miscellaneous causes of death account for this converging of survival rates from the published data. There is heterogeneity among trials concerning what reinterventions are reported and how they are classified but it seems clear that EVAR results in more reinterventions in the long term.

## **2.7. Limitation of Standard EVAR**

As stated, the majority of aneurysms of the abdominal aorta are within the infrarenal portion and as such have a length of aorta that is above the aneurysm but below the renal arteries. The morphology of this length of aorta, termed the neck of the aneurysm, will vary from patient to patient, in terms of its length, diameter, angulation, presence of intraluminal disease such as thrombus or calcification and its shape (broadly speaking the neck is usually either parallel sided or conical becoming wider the closer to the aneurysm it

is). Unless the renal arteries are occluded it is desirable to place the upper most part of the fabric of the stent-graft below the renal arteries so that perfusion is maintained to these vital organs. There are therefore limitations of anatomy within which EVAR can be placed so that adequate fixation and seal are achieved for aneurysm exclusion while maintaining perfusion to the kidneys. These anatomical limitations are outlined in the manufacturers' indications for use (IFU) and are specific to each model of stent-graft. Broadly speaking the manufacturers require a reasonable length of aortic neck (>10mm or >15mm), diameter of aortic neck (<32mm), angulation within the neck (<60° relative to the aneurysm), minimal intraluminal disease and a relatively parallel sided neck. The specific IFU for some devices is discussed in more detail in the Methods section. These anatomical limitations pertain to the neck but there are also limitations relating to the seal zones within the iliac arteries and the 'access' vessels; those vessels through which the device is passed to reach the aneurysm.

Although it is possible to place an EVAR device within an aneurysm that does not exhibit favourable anatomical characteristics as outlined in the IFU there have been studies that have revealed worse outcomes in terms of Type Ia endoleaks and aneurysm related mortality for patients receiving EVAR in these 'hostile' anatomies compared to patients with more favourable anatomy. [78] When presented with hostile neck anatomy therefore alternative treatment options may be explored. These comprise open surgical repair or endovascular repair with advanced stent-graft technologies. Advanced endovascular techniques include:

- Chimney technique – Where an endovascular stent-graft is deployed across one or both renal arteries in order to move the seal and fixation zones to a more desirable part of aorta. Perfusion is maintained to the renal arteries by a separate stent that runs alongside the main stent-graft in the sealing

portion in a downward direction that enters the renal vessel, thereby acting as a 'chimney' to allow blood flow to the kidneys.

- Fenestrated EVAR – A stent-graft that is designed with holes (fenestrations) that align specifically to the ostia of the visceral vessels in a given patient is manufactured. This enables the stent-graft to be deployed more superiorly, extending the seal zone into a long, disease free part of the aorta but maintaining perfusion to the viscerae through fenestrations. Stents are then placed through the fenestrations to secure the stent-graft in place relative to these vessels.
- Branched EVAR – This is usually reserved for true suprarenal aneurysms where the aneurysmal process extends around and above the renal arteries. A stent-graft is deployed within the visceral aorta with perfusion maintained to the visceral vessels by means of covered branches attached to the stent graft. Although similar this is a distinct device with distinct indications from that of fenestrated EVAR.

Of these advanced endovascular techniques, the most commonly utilised method is that of fEVAR and is discussed further in Chapter 3.

## CHAPTER 3 – Fenestrated Endovascular Aneurysm Repair

### 3.1. Introduction

Fenestrated endovascular aneurysm repair (fEVAR) describes a specific type of endovascular device and technique used for endovascular repair of AAA. The aim of fEVAR is to enable endovascular repair of juxtarenal aneurysms that would not be suitable for standard EVAR, specifically those with a short infrarenal neck. The use of a fenestrated stent-graft was first described by Park and colleagues in 1996 [79] after successful introduction of a 'home-made' fenestrated device in two patients. The first commercially available fenestrated device, and still the most widely used, is manufactured by Cook Medical (Bloomington, Indiana, U.S.A.). The device is bespoke for each individual patient and is manufactured according to his or her unique anatomy. Anatomical information is derived from pre-operative non-invasive imaging techniques to accurately delineate the anatomy for each individual patient, in particular relating to the visceral segment of the aorta. The role of fEVAR is specifically to treat AAA that is out with the IFU for standard EVAR in relation to the neck of the aneurysm. It does this by moving the sealing and fixation zone proximally to within the visceral segment of the aorta. This allows aneurysms with necks considered unsuitable for EVAR, because of an inadequate sealing zone below the renal arteries, to be repaired by endovascular means. To maintain perfusion to the visceral vessels, fenestrations are manufactured into the proximal portion of the device that seals within the visceral aorta. The alignments of these vessels vary from patient to patient and hence the need for bespoke manufacture. During implantation the fenestrations are aligned with their corresponding visceral vessel, termed a target vessel, before the stent-graft is fully deployed. The stent-graft is preloaded onto an introduction system to allow delivery of the compressed stent-graft into the circulation before full

'deployment'. The proximal fenestrated portion is loaded onto its introduction system with 'trigger wires' that control the deployment of the stent-graft, as with standard EVAR. In fEVAR an additional trigger wire is in place that controls the release of 'diameter-reducing' ties on the proximal end of the stent-graft. During deployment, diameter-reducing ties continue to constrain the device to less than full expansion so that with partial deployment the device can continue to be manipulated and rotated to align the target vessels with the fenestrations. Once aligned the stent graft can be fully deployed removing the diameter reducing ties. Then additional stents are placed through the fenestrations into the target vessels to further secure the stent-graft in position and maintain vessel patency. These stents protrude from within the aortic lumen, through the fenestrations into the target vessel. The fenestrated device is a modular stent-graft that comprises the proximal, fenestrated portion, the distal bifurcated body, and the iliac limbs. Once the fenestrated portion is deployed the remaining modules of the stent-graft are then deployed in a similar fashion to standard EVAR.

### **3.2. Fenestrated Stent-Graft Technology**

The fenestrated stent-graft manufactured by Cook is based on the Zenith® platform manufactured for use in standard EVAR. It is composed of three components: a fenestrated proximal body, a bifurcated distal body and an iliac leg. It is manufactured from woven polyester fabric, which is hand-sewn to self-expanding stainless-steel Cook-Z® stents. The area in which the IFU for fenestrated devices differs from that of standard endovascular stent-grafts pertains to the aneurysm neck reflecting the rationale that its intended use is to extend the applicability of endovascular repair for juxtarenal aneurysms. The IFU recommends there only need be a minimum of 4mm length of neck inferior to the renal arteries compared with 10-15mm for standard EVAR. However due to the increased complexity of the fenestrated component it does require that there is only a maximum of

45° angulation between the neck and the long axis of the aneurysm as opposed to 60° allowed in standard EVAR.

### **3.2.1. Fenestrated Proximal Body**

This component intends to provide seal and fixation within the visceral segment of the aorta while providing continued perfusion to the visceral vessels. It can do this in one of two ways, a scallop at the uppermost portion of fabric or a fenestration (a hole) within the fabric. At the top of the proximal body there is a bare stent which contains barbs that confer additional fixation of the device in its intended position by engaging with the aortic wall, in much the same way as for the standard endovascular device. There are also radiopaque gold markers placed on the device to aid in the correct positioning under fluoroscopic control and to attain the desired alignment with the target vessels (TV). The following table details the options for target vessel protection available (See table 3.1):

*Table 3.1 Description of Different Mechanisms for Protecting Target Vessels with fEVAR*

Vessel Protection Mechanism	Description	Image
<b>Scallop</b>	<ul style="list-style-type: none"> <li>• Width 10mm</li> <li>• Height 6 – 12mm</li> <li>• Between struts of stent at proximal fabric edge</li> <li>• May be stented</li> </ul>	
<b>Small Fenestration</b>	<ul style="list-style-type: none"> <li>• Width 6mm</li> <li>• Height 6-8mm</li> <li>• Fit between struts of stent within sealing zone</li> <li>• May be stented</li> </ul>	
<b>Large Fenestration</b>	<ul style="list-style-type: none"> <li>• Diameter 8-12mm</li> <li>• Struts of stent may cross opening ('Strut-free' option may also be possible to manufacture)</li> <li>• Not designed to be stented if there are struts</li> </ul>	

The most common architecture for fenestrated devices used is one scallop to accommodate the superior mesenteric artery (SMA) and two small fenestrations, one for each renal artery. However, the devices can be manufactured in a myriad of ways, from providing just one scallop for the lower most renal artery, to four fenestrations for all four visceral vessels (both renal arteries, SMA and Coeliac axis). Small fenestrations are intended to be stented to provide additional fixation of the stent-graft to its deployed position by preventing movement in either a caudal/rostral direction or rotational. Without the additional protection stents provide there is the possibility that target vessels may be compromised, by complete coverage or 'shuttering' of part of the vessel origin by the fabric.

### **3.2.2. Bifurcated Distal Body**

The distal bifurcated body comprises one long limb that engages in one iliac vessel and one short limb that will accommodate the separate iliac leg. The proximal portion of the graft is tubular and is similar to a standard endovascular device with the exception that there is no bare stent above the top of the fabric for added fixation. This is because barbs on the bare stent would engage with the fabric of the proximal fenestrated body and would tear and damage that portion of fabric. The intended deployment of the uppermost part of the bifurcated distal body is within the lower part of the proximal fenestrated portion, with at least a two-stent overlap. This 'overlap zone' and lack of active fixation at this site is intentional because if there were to be caudal migratory forces acting upon the whole system the intention is that the bifurcated distal body should be 'free' to move to accommodate this force. The bifurcated distal body would therefore move but the proximal fenestrated portion would not. Although this may result in component separation and resultant type III endoleak, this may be less disastrous and more easily treated than if the proximal body were to move and compromise the target vessels.

### **3.2.3. Iliac leg**

The iliac leg utilised in the fenestrated device is the same as used in the standard Zenith® platform. It is constructed from polyester fabric sutured to self-expanding stainless steel and nitinol Z-stents. It is delivered and deployed within the short iliac limb of the bifurcated distal body with at least one stent of overlap as recommended in the manufacturer's instructions for use. It then seals within the corresponding iliac artery.

## **3.3. Complications of Fenestrated EVAR**

The complications of fEVAR are the same as those for standard EVAR such as migration and endoleak. However, some complications should be given special consideration with fEVAR.

### **3.3.1. Spinal Cord Ischaemia**

Spinal cord ischaemia can occur after any form of AAA repair. Its exact aetiology is poorly understood but is thought to be multifactorial. It is primarily related to an interruption in the blood supply to the spinal cord, which may be due to; prolonged aortic clamping, intraoperative hypotension, atheromatous embolization and/or interference with pelvic circulation. Spinal cord ischaemia is more common after thoracic aortic aneurysm repair than after AAA repair in part related to the fact that the anterior spinal artery usually, but not always, derives its main blood supply from the lower thoracic aorta.

The rate of spinal cord ischaemia after endovascular repair of a thoracic aneurysm has been reported in up to 9% of patients, and length of aortic coverage has been shown to be a significant risk factor for the development of spinal cord ischaemia. [80] Although this complication is seen rarely in open infrarenal AAA repair (0.26%) and standard EVAR (0.21%) [81] at the outset of the application of fenestrated technology there has been concern that there may be an increased incidence of spinal cord ischaemia owing to the greater length of aortic coverage inherent in fEVAR. In a report from the GLOBALSTAR

collaborators, spinal cord ischaemia was seen in 5 patients out of 318 who underwent fEVAR (1.6%) [82], confirming that although this complication is more common after fEVAR it is still a relatively rare complication. If spinal cord ischaemia develops in the post-operative period prompt recognition and treatment including insertion of a spinal drain and blood pressure manipulation may improve the neurological deficit either partially or totally. Therefore, although uncommon this devastating complication requires careful consideration for those undergoing fEVAR.

### **3.3.2. Target Vessel Loss/Compromise**

Target vessels are at risk of occlusion or compromise both during the initial fEVAR procedure and during follow up. Target vessels may be compromised due to several factors such as:

- 1) Deployment Error – If the graft is deployed inaccurately this may result in shuttering or complete coverage of target vessel ostia. Although in some cases of incomplete coverage it may be possible to ‘rescue’ the situation by placing a stent in the artery and moulding the area with a balloon.
- 2) Embolisation – During manipulation of the stent-graft, target vessel cannulation and stenting it is possible that embolisation of disease present within the visceral aorta or within the target vessel itself may occur. This could result in end organ ischaemia or infarction with occlusion of a branch of the target vessel or the main vessel itself depending on the size of the embolus.
- 3) Angulated neck – If the angulation between the aortic neck and aneurysm is high (>45°), this may lead to distortion of the anatomy in an unpredictable way between the preoperative CT and the anatomy encountered on the day of operation. This can be in part due to the fact the aorta will naturally straighten when the stiff endovascular system is introduced through the lumen, this may then alter the

positions of the target vessels relative to each other and make it impossible to deploy the device preserving all of them.

- 4) Non-stenting – Target vessel loss was noted, particularly in the early days, of fEVAR when in certain circumstances a target vessel was left unstented. During follow up, rotational migration of the stent-graft would eventually cause shuttering or coverage of the target vessel in question causing it to occlude. The recognition of this complication prompted the recommendation that all renal artery fenestrations should be stented. [83]
- 5) Stent-graft migration – Migration in a caudal direction can result in crushing or deformation of target vessel stents sometimes resulting in the need for secondary intervention to rectify the compromise to the vessel. There have been reports that this may lead to loss of the target vessel.[84]
- 6) In stent stenosis – Stenosis within or at the junction of target vessel stent and native vessel may occur during follow up with potential for target vessel compromise or loss.

Although the potential for target vessel compromise and loss is present, according to reports in the literature it is relatively rare. This is likely secondary to the fact that, since its introduction, the complexities of fEVAR are better understood - including the recommendation that all small fenestrations should be stented, and the importance of accurate planning and deployment. Furthermore, for those that do occlude the effects do not seem to be as disastrous as one might expect with a significant proportion having no discernible clinical effect whatsoever. [82, 84]

### **3.4. Follow up after fEVAR**

Follow up after fEVAR is important to detect late complications in the same way as for standard EVAR. Follow up is also designed to survey target vessels and identify if any potential compromise is present that may be amenable to secondary intervention.

The Global Collaborators on Advanced Stent-Graft Techniques for Aneurysm Repair (GLOBALSTAR) project has been set up on behalf of the British Society for Endovascular Therapy (BSET) to act as a registry of all fenestrated stent-grafts implanted within the UK. In the absence of randomised controlled trials the aims of the project at the outset were to evaluate the technique in terms of primary and secondary endpoints, establish an archive of all pre-operative and follow up imaging, to aid detection of mechanisms of failure, and to provide an “early warning system” for complications specific to the technique.[85] In 2012 the first results from the registry were published for fEVAR confirming the safety, efficacy and feasibility of this technique reporting on 318 patients who received fEVAR in the UK. [82] The database is maintained and populated with data by physicians performing the procedures from across the UK and is the only such registry for fEVAR worldwide.

### **3.5. Treatment of juxtarenal aneurysms**

Although fEVAR has extended the applicability of endovascular repair to juxtarenal aneurysms its increased complexity inherently brings greater potential for devastating complications, such as visceral vessel loss, morbidity and mortality. It is however important to note the flaw in the comparison of the treatment of infrarenal aneurysms that receive standard EVAR with juxtarenal aneurysms that receive fEVAR, as these are two different technologies and arguably two distinct versions of the same disease. Juxtarenal aneurysms may be considered a distinct entity as the options for repair are distinct from those for a simple infrarenal aneurysm; in open repair of a juxtarenal aneurysm the aortic cross clamp would usually be placed above one or both renal arteries and sometimes higher, above the

SMA or coeliac axis. The level of clamp site has been shown to effect the outcome after open aneurysm repair confirming that juxtarenal aneurysms pose a greater risk, in terms of short term mortality, than their infrarenal counterparts when undergoing open repair. [86] This furthermore reinforces the need for anatomical distinction between these two entities.

The term 'juxtarenal' aneurysm is defined within reporting standards from the society of vascular surgeons (SVS) in the United States as an aneurysm that has "no normal aorta between the upper extent of the aneurysm and the renal arteries". [87] This definition has not changed since 1991 and the interpretation of its meaning is variable across the literature. There is discrepancy about whether it truly means "no normal aorta" or whether a very short length of "normal" aorta would qualify. Some interpret to mean that only those patients in whom an aortic cross clamp would not be placed below both renal arteries fit the definition. The reason for this is probably that until the endovascular era a precise definition of a juxtarenal aneurysm was not necessary. In any case the term juxtarenal aneurysm is delineated from an infrarenal aneurysm primarily in the length of aneurysm neck that is present below the renal arteries. It is reasonable to suggest a new definition of 'juxtarenal' aneurysm that is fit for the endovascular era. The suggestion is that the new definition should utilise the limits of IFU for standard EVAR to define a juxtarenal aneurysm, i.e. an aneurysm that is not suitable for standard EVAR (according to its IFU), this could be termed – a non-standard aneurysm.

The utilisation of such a definition is clear-cut and easily applied to all aneurysms as the anatomical measurements can be made from a pre-operative CT scan. The treatment options for such an aneurysm would therefore be; open repair, standard EVAR (placed outside of IFU) or advanced stent graft techniques (such as fenestrated or chimney EVAR). Importantly however there have been no randomised controlled trials to investigate these

various options for treating a non-standard aneurysm and as such the clinical outcomes for each method are largely unknown with respect to each other.

## CHAPTER 4 – Rationale and Design of Study

### 4.1. Introduction

Although there has been randomised clinical trials assessing the treatment options for standard infrarenal aneurysms [64, 72, 73, 88], namely standard endovascular repair versus open repair, there has been no such randomised controlled trial of the treatment options for juxtarenal aneurysms. The treatment options for these aneurysms include open repair and endovascular repair. The most commonly used method of endovascular repair specifically designed for treatment of juxtarenal aneurysms is fenestrated endovascular repair. The safety, feasibility, efficacy and mid to long term results of fEVAR have been well documented and show a technique that has acceptable rates of mortality and success in the short term as well as acceptable rates of complication and target vessel loss in the longer term. [82, 84, 89-92] There are alternative options of endovascular repair of juxtarenal aneurysms and one commonly used method is applying standard EVAR, used outside its indications for use (IFU) within anatomy that it is not designed to treat i.e. a juxtarenal or short neck infrarenal aneurysm. However, the data comparing fEVAR with this and other treatment strategies is scarce and requires further review.

The aim of this study therefore was to investigate these treatment options for juxtarenal aneurysms and specifically compare the clinical outcomes of conventional open surgery, EVAR used outside IFU and fEVAR for juxtarenal aneurysms within a defined geographical region, in terms of perioperative mortality, mid to long term survival and clinical success (as defined in the reporting standards for endovascular repair[93]. The defined geographical region in question is the Cheshire and Merseyside region.

For standard infrarenal aneurysms it is relatively well understood from the gathered evidence that EVAR confers a short-term benefit over open repair in terms of perioperative mortality, but this advantage appears to equalise over time. The compromise for this early

advantage is an increased risk of late failure and need for reintervention in the future. The decision-making process for individual patients is therefore relatively well understood and can be explained to them. For juxtarenal aneurysms however the differences in perioperative mortality (if there are any) are not as well understood and likewise the long term outcomes in terms of mortality, need for reintervention and rate of late failure i.e. the 'compromise' of endovascular repair – in comparison to open repair is much less understood and therefore the weighing of advantages and disadvantages of any given treatment for a particular patient are less well understood. It is the desire to understand better these differences for juxtarenal aneurysms, and thereby improve the evidence base that informs the decision-making process for individual patients that provides the rationale for this research. In essence – for those patients that are out with the treatment of standard EVAR or infrarenal open repair (which is usually because of an unsuitable infrarenal neck – making them juxtarenal aneurysms) what are the advantages and disadvantages of the three most common treatment strategies? To investigate this question the following hypothesis and study were designed.

#### **4.2. Hypothesis:**

It is proposed that an endovascular solution to repair juxtarenal aneurysms would have superior outcomes in line with what is seen in the RCTs of standard EVAR. Furthermore, fenestrated EVAR is specifically designed to treat these types of aneurysms to ameliorate the risk of late failure whereas standard EVAR is not – it is therefore also proposed that fEVAR will have superior outcomes of the three treatments. The terminology of non-standard aneurysm will be used to replace the term 'juxtarenal' to specifically define the anatomy that is related to. These proposals generated the following hypothesis:

Fenestrated Endovascular Aneurysm Repair (fEVAR) has superior clinical outcomes as a treatment strategy for non-standard AAAs that are unruptured in whom aneurysm repair is deemed to be more beneficial than conservative management.

The term “superior clinical outcomes” is in relation to all cause and aneurysm related mortality at all time points both perioperatively and throughout follow up. For the purposes of the hypothesis these primary outcome measures carry an equal weighting towards the definition of “superior clinical outcomes” to reflect the need for aneurysm repair to prevent death both in the short and longer term. Aneurysm related, and all-cause mortality are equally weighted to reflect the desire for any given treatment option to be superior to its alternatives both in improving survival from the condition and in providing an overall benefit to any given patient. This is because, for an individual patient, mortality has the same devastating effect whether it is caused by the aneurysm or not. It remains important however to demonstrate (if possible) that a treatment reducing mortality from the condition it is treating regardless of all-cause mortality which inevitably is influenced by unrelated confounding factors. Other clinical outcome measures that will be considered to contribute to whether fEVAR is “superior” will be technical success and clinical success as defined by agreed reporting standards.[93] These outcome measures will inform the decision of whether the hypothesis is satisfied or not and to reflect the importance of continued clinical efficacy throughout follow up clinical success will have a greater weighting to technical success in making this decision but less of a weighting than the outcome measures related to mortality. This reflects the fact that each of these represents the ability of the method of repair to exclude the aneurysm from the circulation without demonstrable major consequences that potentially affect the patient’s quality of life in a measurable and quantifiable way.

### 4.3. Definition of non-standard aneurysm

In order to examine the clinical outcomes of fEVAR and its alternative treatment options it is important to define the cohort of patients being studied so that similar anatomical characteristics apply for all patients regardless of the treatment they have undergone or are due to undergo. Essentially, as with any clinical research, an attempt to control for confounding factors is important to increase the applicability and validity of the results for the population as a whole. By its nature fenestrated endovascular repair is reserved for patients with an aneurysm that extends close to the renal arteries. It was specifically developed and designed for this purpose. Studies comparing standard EVAR stent grafts have shown that decreasing neck length between the renal arteries and the top of the aneurysm correlate to worse clinical outcomes in terms of higher perioperatively mortality [68], increased aneurysm related mortality over follow up [94], Increased perioperative type 1a endoleak rate [68, 95] and perioperative reintervention rate [96]. Therefore, when comparing treatment options, one should be careful to define and report the anatomy of the patients being studied as this seems to be an important confounding factor that affects relevant and commonly used clinical outcome measures. The desire to find efficacious and durable treatment for those patients with shorter necks culminated in the development and use of fenestrated (and other advanced endovascular) technology. The IFU for the Zenith fenestrated device is similar to that of the standard Zenith stent-graft with the notable exception that the fenestrated device can be used for aneurysms with an infrarenal neck length of 4mm or more compared to 15mm or more. In order to compare this technology with alternative treatment strategies one should therefore aim to compare like for like anatomy. Although this may sound a simple proposition in principle, in reality it is more complex.

The starting point therefore in the design of this study was to define the patient population being studied. The definition of juxtarenal is relatively loose and is used interchangeably with the definition pararenal. As stated earlier when reviewing the literature, the term juxtarenal can relate to a 'short' neck, no neck, a neck which requires suprarenal clamping and is therefore an imprecise term. For the purpose of this study it was important to develop a new term that specifically defines the anatomy of interest and the patient population being studied. The patient population of interest was patients that were not suitable for standard endovascular repair according to anatomical criteria pertaining to the infrarenal neck. The term non-standard aneurysm/non-standard anatomy was developed to describe any anatomy of the infrarenal neck that fell out with standard EVAR indications for use.

Stent-graft devices used to treat infrarenal abdominal aortic aneurysm by EVAR have specific instructions for use that accompany each device. These are instructions from the manufacturer about various aspects of the use of each device. They generally include a description of the device, indications for its use, contraindications, specific warnings and precautions related to the implantation of the device, reported adverse events associated with its use, advice on patient selection and treatment and how to physically use or 'deploy' the device. Included within the instructions for use are detailed indications for use (IFU). The IFU details specific pre-operative anatomical criteria that an aneurysm must adhere to in order that the device is used according to each manufacturer's intention. The specific anatomical criteria include the diameter, angulation and length of the infrarenal neck along with other criteria. If an aneurysm possesses anatomy that violates any of these criteria and the device implanted anyway then this would be considered 'off-label' use of the device. The defined parameters for the indications for use were determined from preclinical engineering studies and clinical trial results for endovascular repair as a whole

and for specific devices. [97] The term 'instructions for use' is often used in both everyday clinical practice and the wider literature when 'indications for use' is intended.

As stated above the outcomes for patients treated by standard endovascular repair and open repair for infrarenal aneurysms are well known due to numerous randomised controlled trials in this area. For inclusion into the randomised controlled trials patients' anatomy was assessed to determine whether it was suitable for endovascular repair with a standard device before the patient could be randomised to either EVAR or open repair. In the UK EVAR Trials [64] there was no specific anatomical cut off that was defined as making a patient suitable or not for EVAR. However, all aneurysms were assessed by a radiologist and specifically the question was asked whether the "aneurysm neck dimensions are suitable for EVAR?" taking into consideration, length, diameter, angulation and thrombus. The majority of devices implanted in that study were one of the following three – 51% Zenith (Cook, Copenhagen, Denmark), 33% Talent (Medtronic, Minneapolis, MN, USA), 7% Excluder (Gore, Flagstaff, AZ, USA). At the time of the EVAR trials IFU relating standard EVAR was specific to the device used but in general the infrarenal neck should be  $\geq 10\text{mm}$ , with a diameter  $< 28\text{mm}$  and angulation  $< 60$  degrees. It is not possible to state from the published articles on the UK EVAR trials exactly what the anatomies being treated was, but it is reasonable to assume the vast majority of patients treated fell within these IFU criteria. Therefore, the use of non-standard anatomy to define the anatomy of a patient population specifically defines those patients not treated within the RCTs and helps to answer the question posed by the hypothesis stated above.

Therefore, in the design of this study it was decided that the anatomical criteria for inclusion were that patients should have an infrarenal neck that violates the IFU for standard EVAR, i.e. 'non-standard aneurysms'. There are many different manufacturers of stent-grafts, each with their own similar but specific IFU and therefore to simply define

non-standard anatomy as that which is ‘outside IFU’ for standard EVAR is too simplistic and would create confusion but this is the essence of the definition.

To define non-standard anatomy the IFU of three commonly used stent-grafts within the Cheshire and Merseyside region were identified and scrutinised. The anatomical criteria to define a non-standard aneurysm were drawn from these specific manufacturers IFU. The three stent-grafts in question were: the Endurant Stent Graft System (Medtronic, Inc. Minneapolis, Minnesota, U.S.A.), the Zenith Flex AAA Endovascular Graft (Cook Medical, Bloomington, Indiana, U.S.A.) and the Gore Excluder AAA Endoprosthesis (W.L. Gore & Associates, Inc. Flagstaff, Arizona, U.S.A.).

Table 4.1 below details the manufacturers recommended IFU anatomical criteria that were present in the years of the study:

*Table 4.1 Stent-Graft IFU from Manufacturers*

Type of Device	Endurant		Zenith Flex	Gore Excluder
Infrarenal neck length (mm)	≥ 10	≥ 15	≥15	≥15
Infrarenal neck diameter (mm)	19 – 32	19 - 32	18 - 32	19 – 29*
Suprarenal aortic angulation	≤45°	≤60°	<45°	NS
Infrarenal aortic angulation	≤60°	≤75°	<60°	≤60°

Table 4.1 - Diameter is measured outer wall to outer wall unless otherwise stated. \* = measured inner wall to inner wall, NS = Not stated

The Endurant stent-graft is unique among the three in that the criteria for angulation are dependent on the neck length as can be seen from the table. If the neck length is 15mm or greater then a greater degree of aortic angulation can be treated ‘within IFU’. If the neck length is between 10 and 15 mm then the recommendations from the manufacturers is that less angulation should be present. It is important to note that the stent-graft remains the same design and manufacture, but it is simply the criteria for what is recommended as acceptable anatomy that changes. Suprarenal aortic angulation termed the alpha ( $\alpha$ )

angulation is defined as an angle relative to the axis of the suprarenal aorta. Infrarenal aortic angulation, termed the beta ( $\beta$ ) angle is defined as the angle relative to the long axis of the aneurysm.

If an aneurysm was treated with a specific endovascular device and the anatomy was in breach of the IFU for that device in any way, then it was deemed non-standard. This would therefore capture all patients who were treated with a standard EVAR device 'off – IFU'. If the patient did not receive a standard endovascular device then their anatomy would only be considered non-standard if none of the above devices could be placed within IFU. For example, in someone who has not had an endovascular repair a neck length of 9mm would qualify the aneurysm as non-standard but not, necessarily, a neck length of 11mm (because the Endurant device can be used in neck lengths  $\geq 10$ mm, as long as angulation is acceptable). In order to exclude patients that possessed a thoracoabdominal aneurysm and one that would traditionally necessitate placement of a branched endovascular stent-graft if treated endovascularly it was deemed that if an aneurysm possessed a neck diameter of  $>36$ mm immediately below the level of the renal arteries then this would exclude it from the definition of a non-standard aneurysm and instead it would be defined as a thoracoabdominal aneurysm.

In the design of a study one could propose to include all patients, treated by any method with a neck length of  $<10$ mm and exclude those with a neck length of  $>10$ mm. Although this would have the value of simplicity it may not include several patients with other adverse anatomical characteristics that would be relevant to this research. It would also ignore the important confounding factor of stent-graft device and its potential effect on outcome. Since different stent grafts have different anatomical thresholds set in their IFU a single cut off value could include some who were in IFU or exclude some who were out of IFU depending on the threshold set. As stated before if the threshold is set so that all stent

grafts included are out with the IFU for only one anatomical variable then this potentially excludes some who are out of IFU for another characteristic. Therefore, not including an important part of the population in whom fEVAR would be a realistic alternative treatment option. The premise of this research is to compare fEVAR with alternative treatment options and conversely to compare those alternative treatment options with fEVAR. In order to do this anatomical inclusion criteria must allow for the flexibility in differing IFUs between device manufacturers. This accepts and takes account of the fact that some patients included, who are out of IFU for a device implanted, could have been potentially treated within IFU by an alternative standard device. This considers the fact that stent-grafts differ in their design and manufacture and accepts the supposition that for any given device there are assumed tolerances of anatomy that it can treat effectively.

Utilising IFU as a threshold in itself, although more complex, does allow the inclusion of patients that may have been treated within IFU by a different device. Furthermore, the research will explore and investigate whether 'IFU' is a useful and valid indicator of anatomy and whether being inside or outside 'IFU' equates to better or poorer outcomes. This would be important for ongoing and future research because technology is continually evolving and the IFU evolves with it, using IFU as a bench mark will ensure that patients can be compared irrespective of what device was placed. It may be that this research shows that 'IFU' is not a useful marker for the thresholds of anatomy treatable, which would be useful information also both for manufacturers and clinicians. In order to make them both consider again why the anatomy thresholds in the IFU are what they are, and should they be any different.

An alternative method would be to employ a stratification of anatomy either based on anatomical values or IFU criteria. Some studies [68, 98] have successfully employed both methods by investigating outcomes for necks <10mm, 10 – 15mm and >15mm in length.

And conservative, liberal and time dependant IFU, which essentially alters the number of patients who were definitely out of IFU included in the study population. What is notable about both these studies however is that they were large database studies analysing data from thousands of patients enabling meaningful conclusions to be drawn from stratification because each group still had a considerable number of patients within it. As in this study and most published studies the numbers are relatively small and do not allow multiple groups to be created.

In this study then the definition of non-standard aneurysm applies to any aneurysm that exhibits any one of the following criteria:

- 1) Any aneurysm with an EVAR device placed outside IFU

By deductive reasoning;

- 2) A neck length of <10mm
- 3) An alpha angle of > 60 degrees
- 4) A beta angle of >75 degrees.
- 5) Neck diameter >32mm (but  $\leq$  36mm)

Moreover, if the neck length is 10 – 15mm AND one of the following apply then it is non-standard:

- 1) Alpha angle >45 degrees
- 2) Beta angle >60 degrees.

In summary the definition of a non-standard aneurysm is those that are out with the IFU for standard EVAR but within that for fenestrated EVAR. Once the definition was decided the design of the study could begin.

#### 4.4. Study Design

The chief investigator was responsible for the design of the study. No expert methodological or statistical support was sought at the design stage of the study. There had been no prior pilot study performed either. The design of the study began in 2012, first with the hypothesis and then with the definition of non-standard aneurysm.

In order to investigate the hypothesis, the study proposed contained four main parts:

1. A Systematic Review of the Literature to investigate the outcomes for patients with non-standard aneurysms undergoing standard EVAR, open repair and fenestrated EVAR
2. A retrospective single centre review of clinical outcomes following fEVAR
3. A Multicentre retrospective concurrent cohort study of patients undergoing aneurysm repair with non-standard anatomy
4. After initial analysis and review a decision was made to also include a retrospective analysis from a single centre of the clinical outcomes for patients undergoing standard EVAR or open repair for patients with standard anatomy. Primarily this study would act as a control group for the multicentre retrospective study of non-standard aneurysms.

The second part of the above four parts, the retrospective single centre review of fEVAR would identify patients from a departmental database and national registry and document clinical outcomes after fEVAR to provide a background of overall outcomes after fEVAR at the base site where the research was conducted. It is important to note that the specific anatomy of each fEVAR case would not be reviewed in the retrospective single centre review – this was for two primary reasons; firstly, the review is designed to investigate outcomes after fEVAR as a specific treatment rather than focus on anatomy alone. Secondly the use of fEVAR within the Royal Liverpool University Hospital (base site) goes

back to 2003 and it would have been practically impossible to obtain all CT scans for all those patients to review their anatomy. This aim of this study was to obtain results of a large number of fEVAR patients to understand better the short, mid-term and longer-term outcomes for patients undergoing fEVAR regardless of their anatomy. The study was therefore concerned with and centred around a specific treatment rather than a patient cohort.

The multicentre retrospective concurrent cohort study of non-standard aneurysms would form the basis of the research and be the primary study. This study, unlike the single centre review of fEVAR patients, would aim to study patients with a specific anatomy rather than focussing on a treatment option. The idea was to identify all patients with non-standard anatomy that undergo operative intervention to treat their aneurysm and investigate the clinical outcomes. Therefore, the population of interest is defined by their anatomy as a starting point rather than anything else. Once the anatomy was defined all patients who fell within the definition of that anatomy (non-standard) would be considered for inclusion into the study. Ideally the study would have included all non-standard aneurysms that were considered for an operation whether eventually operated on or not however there was practically no way to identify these patients as no database of patients 'turned down' for aneurysm repair was kept at any of the hospitals included in the study. If these patients could have been identified and included, it would give a more complete picture of the outcomes of all patients with non-standard aneurysms and provided valuable data with regards to the natural history of this specific type of AAA. The study is designed to consider all patients from across the Cheshire and Merseyside area. This was for two reasons; to try and increase the number of patients for analysis to increase the validity of the results but also to include patients treated at different types of institutions. The reason it is important to include patients from a number of hospitals (small and large district general hospitals as well as large tertiary referral teaching hospitals) was to try and broaden the applicability of

the results to a general population of patients rather than including only those treated at the base site (a large tertiary referral centre) – if this is done inevitably there would be an element of selection bias inherent in the type of case seen and treated at such an institution. So, this decision in the design of the study was to try and reduce the effect of this confounding factor.

In designing this study consultant vascular surgeons at the Royal Liverpool University Hospital were asked about practices within their tertiary vascular unit for treatment of non-standard aneurysms. This essentially identified that there would be three categories of patients: those treated by traditional open operation, fEVAR, and a standard EVAR performed outside of IFU. A preliminary literature search was conducted by the chief investigator but there was little evidence identified that could help determine the principal outcome effects for the different methods of repair. Therefore, no power calculations or sample size calculations were done due to a lack of reliable pilot data. There was no accurate record of the number of aneurysm repairs or the proportion that were non-standard at the beginning of the study. Preliminary calculations based on activity at the Royal Liverpool University Hospital for fenestrated endovascular and standard endovascular aneurysm repair estimated that to identify approximately 150 – 200 patients with a non-standard aneurysm in total 500 – 600 aneurysm repair patients would need to be identified. In order to identify this many patients it was deemed necessary that patients would need to be identified over the entire Cheshire and Merseyside region and be from a two-year period of activity. The other advantage of conducting a multicentre study would be that the results of the study would be able to be generalised to a wider population primarily because the Royal Liverpool University Hospital (base site) was an expert tertiary referral centre. By including other hospitals in the region activity within district general hospitals would also be captured.

It was therefore decided that analysis of all patients who underwent aneurysm repair for a 'non-standard aneurysm' in the Cheshire and Merseyside region in the 24-month period 1<sup>st</sup> April 2006 – 31<sup>st</sup> March 2008 were to form the basis of data for this study. The time period was chosen because the introduction of the electronic storage of radiological images on the picture archive and communication system (PACS) began in 2006 and it was envisaged that this would enable the chief investigator to perform core laboratory analysis of all CT scans of aneurysm repair patients as the images could be digitally transferred.

There were seven centres within the Cheshire and Merseyside region that performed at least one of the three treatment methods during the study period. These included; the Royal Liverpool University Hospital, Aintree University Hospital, Southport Hospital, Warrington Hospital, Arrowe Park Hospital, Countess of Chester Hospital and Leighton Hospital. Therefore, during the design of the study, the lead consultant vascular surgeon at each site was contacted to consent for a retrospective analysis of patients at their site to be conducted and to act as a point of contact for the chief investigator at the site. It was envisaged that although the chief investigator would need to visit each site initially to identify patients and then once again to review clinical notes, the transfer of data could happen electronically and therefore there wouldn't need to be a permanent researcher at each site.

#### **4.4.1. Inclusion criteria:**

Inclusion and exclusion criteria were defined during the design of the study as follows. Patients with a 'non-standard aneurysm' of their abdominal aorta who underwent repair within one of the centres listed above and within the above time period. Patients must have had a CTA of their abdominal aorta prior to the aneurysm repair that could be reviewed on a 3-dimensional workstation and be of satisfactory quality to allow for detailed anatomical measurements.

#### **4.4.2. Exclusion criteria:**

All patients with previous surgical or endovascular repair of an abdominal aortic aneurysm were excluded. As well as any patients who were haemodynamically unstable or undergoing repair for a leaking or ruptured aneurysm. Patients who underwent 'branched' endograft technology as opposed to fenestrated EVAR were excluded as this method of treatment is recognised to be entirely distinct from fEVAR and EVAR.

#### **4.4.3. Identification of patients**

To try and identify the maximum number of patients for inclusion as possible multiple sources would be used to identify patients. Office of Population Censuses and Surveys (OPCS) codes would be used at every site to identify patients 'coded' as having some form of aneurysm repair within the specified time period. To identify further patients suitable for inclusion the intention was also to access theatre records of aneurysm repair, departmental databases and individual surgeon databases at each hospital.

#### **4.4.4. Study Protocol**

Before ethics approval could be gained a detailed protocol for what variables would be collected during the study and how this would be done was drawn up. Defined pre-operative, intraoperative and anatomical variables would be collected. Furthermore, post-operative clinical outcomes and follow up data from patient case notes, laboratory results, clinic letters and follow up medical imaging would be collected. A proforma was developed to assist with the data capture. Data points and information collected will be described in more detail in the methods section. The intraoperative details to be collected were derived after reviewing published reporting standards for endovascular repair [93, 99]

#### **4.4.5 Pre-operative Anatomical Characteristics of the Aneurysm**

One area of the study protocol that merits specific mention is the method by which anatomical measurements of an included aneurysm would be made. The measurement

protocol for anatomical measurements was designed after the chief investigator was trained in the use of software and aortic CT measurements. The chief investigator was trained by a consultant vascular and endovascular surgeon working at the Royal Liverpool University Hospital. The methods for measurement were used by that consultant in his routine clinical practice and where necessary those methods were standardised to provide a reliable and reproducible way of measuring the anatomy. Ten 'test' scans randomly chosen from the departmental database were measured by the chief investigator initially to identify potential pitfalls when measuring and to inform the development of the measurement protocol. There was no intention of using these 'test' measurements to validate a method of measuring, they were simply to aid the training of the chief investigator and to inform the development of the measurement protocol. At the time of the design of the measurement protocol (early 2012) no comprehensive, validated and agreed protocol was found to exist from a search of the literature. There were some reports and studies of isolated anatomical features but no comprehensive reports. The measurement protocol was set out at the beginning of the study and is described in detail in the methods section of the non-standard aneurysm study.

#### **4.4.6. Ethical Approval**

Ethical approval was not needed for the retrospective review of single centre data for fEVAR. However, to conduct the multicentre retrospective study of non-standard aneurysms ethical approval was needed. A detailed account of the process of ethical approval is included in the methods section for the relevant study later.

#### **4.4.7. Outcome measures**

For the non-standard aneurysm study the primary and secondary outcomes were decided after review of the published reporting standards and literature review:

Primary Outcome Measures:

- 30-day mortality/In-hospital mortality
- Mid-term mortality and aneurysm related mortality
- Technical success
- Clinical Success

Secondary outcomes:

- Visceral vessel patency
- Renal insufficiency and need for dialysis
- Re-intervention rates, both surgical and endovascular
- Conversion to open repair
- Major complications

### **4.5. Summary of Chapter 4**

This chapter details the design of the current study which the primary part of is the retrospective review of clinical outcomes for non-standard aneurysms treated by open repair, fEVAR or EVAR outside of IFU. More details regarding the methodology of that study are detailed later. To reiterate, in order to investigate the hypothesis, the study proposed contained four main parts:

1. A Systematic Review of the Literature to investigate the outcomes for patients with non-standard aneurysms undergoing standard EVAR, open repair and fenestrated EVAR
2. A retrospective single centre review of clinical outcomes following fEVAR
3. A Multicentre retrospective concurrent cohort study of patients undergoing aneurysm repair with non-standard anatomy
4. After initial analysis and review a decision was made to also include a retrospective analysis from a single centre of the clinical outcomes for patients undergoing standard EVAR or open repair for patients with standard anatomy. Primarily this study would act as a control group for the multicentre retrospective study of non-standard aneurysms.

The analysis of clinical outcomes for standard aneurysm patients was conducted in the same way as that for non-standard patients with the exception that patients were only identified from one site, the base site (Royal Liverpool University Hospital). The remainder of the study protocol was carried out for those patients in exactly the same way including data capture and anatomical measurements. The intention is that this supplementary analysis would provide a control group for two of the interventions (EVAR and open repair), as by definition, fEVAR is not used in standard anatomy patients. It would also allow a deeper analysis of the outcomes for the patient population.

## **5. CHAPTER 5 – Systematic Review of Clinical Outcomes Following Placement of Standard EVAR stent Graft in Non- Standard Anatomy**

### **5.1. Introduction**

The randomised controlled trials detailed above confirmed the benefit of endovascular repair compared with open repair, in the short term at least. By necessity the patients enrolled to these trials met had to be ‘anatomically suitable’ for endovascular repair. The definition of anatomic suitability has evolved since the inception of EVAR. Early in the use of EVAR, in the mid to late 1990s, ‘recommended guidelines’ [97] were used to define anatomic suitability. These guidelines were ‘derived from clinical experience, intuition, and mechanical and physical principles’ in the case of the development of the Cook Zenith bifurcated graft. Benchtop models and laboratory engineering testing provided insight to inform the guidelines to be applied to that particular device. [100] With the approval of a number of endovascular stent graft devices in 1999 by the US Food and Drug Administration (FDA) device specific anatomical indications for use became clearly documented. Since then new and updated iterations of earlier stent graft designs have come to the market. With this technological evolution there has been expansion of the anatomy detailed in devices indications for use to allow treatment of a larger proportion of patients.

The most common reason an aneurysm may not be suitable for endovascular repair is secondary to the aortic neck anatomy [101, 102]. Inevitably with additional experience with endovascular technology physicians expanded their treatment to include a proportion of patients who had anatomy outside the IFU for endovascular repair. With most of these

exhibiting features within the aortic neck considered to be less favourable to the performance of the standard endovascular stent graft. The advent of more complex endovascular technology and techniques such as fenestrated, branched and chimney endovascular repair were developed precisely to tackle the problem of patients who exhibited anatomy not suitable for standard endovascular aneurysm repair. They primarily achieve this by moving the seal and fixation zone of the 'stent-graft complex' more proximally, into the visceral segment of the aorta. This is to distance the proximal end of the stent graft away from 'hostile' anatomical features and into supposed healthy aorta – with the aim of providing a more durable proximal seal and fixation. The desire to achieve a durable seal and fixation proximally is because failure at this point of the interaction between 'stent graft complex' and native anatomy probably leads to the most dangerous sequelae, both in terms of clinical outcomes and for the resultant available treatment options available to solve the problem. The primary complication in this regard is type 1a endoleak which exposes the patient at significant increased risk of aneurysm rupture. However, there are significant disadvantages to advanced endovascular techniques including the need to 'instrument' and stent visceral vessels with potential serious complications from this. The use of custom made fenestrated or branched devices require several months to be manufactured and delivered. There is often a significant increase in cost with the use of these advanced devices and techniques. It is therefore understandable then that physicians would want to be able to place standard endovascular stent grafts even in anatomy that is considered outside the instructions for use as long as the resultant clinical outcomes are not deleteriously affected. During the evolution in practice of EVAR there has been debate at where the limit of anatomy is that can be successfully repaired with a standard EVAR stent graft. Therefore, it is important to understand what the risks and complication of using standard endovascular devices in patients with 'hostile' anatomy are to enable a full understanding of the treatment options available and whether the

shortcomings of standard EVAR used out of IFU result in more deleterious effects for the patient than advanced endovascular techniques or indeed open repair.

EVAR used outside IFU has been associated with increased technical failure [103], type 1 endoleaks [94, 104] and increased secondary interventions [67, 103] However some studies have reported equivalent rates of clinical outcomes both in the short and long term for patients treated when outside IFU compared to those treated within IFU [105, 106] There is therefore continuing debate about how far this technology can truly be pushed. Two systematic review and meta-analyses have been published in this area [78, 107] the most recent in 2013. The conclusions from those meta-analyses were that EVAR placed in unfavourable proximal neck anatomy led to an increase in the number of adjunctive procedures needed, 30-day morbidity, rate of type I endoleak development, secondary procedures needed and aneurysm related mortality within 1 year. However, their conclusions were not consistent across all these areas. There has been continued advancement of endovascular technology in the intervening years with publication of larger datasets since these systematic reviews and therefore the aim in this systematic review was to provide an updated synthesis of the available evidence and to use the larger number of studies published in this area to try and limit any potential bias or confounding factors that may have been present in earlier reviews.

The question being addressed in this systematic review is to understand what the clinical outcomes are for patients undergoing Endovascular Aneurysm Repair using a standard stent-graft whom exhibit proximal aortic neck anatomy that is considered outside the indications for use for the implanted devices. The primary clinical outcome measures will include the following both perioperatively and throughout follow up; all-cause mortality, aneurysm related mortality, reintervention rates and graft related endoleaks. Secondary outcome measures will include: primary and primary assisted technical success, endograft

migration, visceral vessel patency, rates of conversion to open repair, rates of renal dysfunction, aneurysm expansion throughout follow up. The systematic review also aims to investigate by its narrative nature the question of whether investigation of specific anatomical values or “outside IFU” anatomy is a more valid and useful method of investigating clinical outcomes for patients with “hostile” anatomy. Specific anatomical values would relate to defined criteria such as a specific value for neck length or angulation, with the advantage that the criterion would be applicable to all aneurysms in the same way regardless of which EVAR device is placed. “Outside IFU” anatomy is a more abstract concept but potentially has the advantage of looking at anatomical criteria more holistically and using IFU as a benchmark for what constitutes “good” or “bad” anatomy. It may limit applicability of results to only the stent-grafts studied.

Patients who undergo implantation of a standard stent-graft out of IFU with regards to proximal neck anatomy will be considered. In studies where there is also a comparator group of ‘in IFU’ patients receiving standard EVAR, their clinical outcomes will be assessed and used as a reference point for clinical outcomes. Through this report patients who have a standard stent graft placed in anatomy that is considered out of the IFU, “hostile” or “complicated” anatomy as per the inclusion criteria will be termed non-standard anatomy (NSA) patients. Those with anatomy conforming to IFU criteria will be termed standard anatomy patients (SA). It is expected that no randomised controlled trial will be identified and as such cohort and case series studies whether retrospective or prospective will be included.

## 5.2. Methods

The systematic review followed reporting guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) document. [108] In line with these guidelines a protocol for the systematic review was established prior to the beginning of the literature search as follows. The protocol is reproduced here in its entirety.

### 5.2.1. Protocol for Systematic Review, Including Eligibility Criteria

With increased use of fenestrated endovascular aneurysm repair and the knowledge that clinical outcomes in terms of short- and long-term mortality are worse for fEVAR compared with standard endovascular aneurysm repair it is important to define the published outcomes for these patients and comparing these outcomes to valid alternative treatment strategies. Since aneurysms treated “on-label” with standard EVAR represent a distinct anatomical entity compared to those treated with fEVAR it is important to understand the outcomes for EVAR when used in anatomically similar patients – i.e. EVAR outside of IFU. This will help inform the debate about the best treatment option for non-standard aneurysms.

A systematic review of the literature will be undertaken to examine the clinical outcomes for patients undergoing abdominal aortic aneurysm repair for non-standard aneurysms using standard EVAR. Non-standard aneurysms are defined as those in which the aortic neck anatomy is considered outside indications for use (IFU) criteria for standard infrarenal EVAR. Primarily this includes those aneurysms with a neck length of less than 10mm from the lowermost renal artery ostium to the top of the aneurysm, neck diameter of >32mm and or angulation of >90 degrees between the infrarenal neck and the aneurysm itself. An aneurysm would be considered non-standard if any of these criteria are present. Additionally, if a specific device was used and it is stated explicitly that the aneurysm

treated was outside the IFU for that particular device then this would also be considered “off-label” use of standard EVAR and these studies would be included in the systematic review. It is important to note that different devices from different manufacturers may have different anatomical criteria included in their IFU. Although the above anatomical characteristics encompass the restrictions set out in the IFU for most stent-grafts there are some in which their IFU does not exclude more extreme anatomies than that stated above. In that scenario the IFU for the stent graft being studied will be used to determine whether patients have had stent grafts placed in anatomy that is outside the IFU for the device used. The objective of the systematic review is to compare the published literature for all patients with non-standard aneurysms undergoing standard EVAR. It is expected that no randomised controlled trials would be identified and therefore non-randomised studies evaluating clinical outcomes for standard EVAR placed out of IFU would be included in the analysis.

Inclusion criteria:

- Aneurysm morphology - For a study to be included in the analysis, it should clearly state that the population had morphologic infrarenal neck characteristics that were not within the indications for use for standard EVAR. As already stated, the IFU for the specific device (or devices) used would be used to determine if the patients had a non-standard aneurysm or not i.e. the aneurysm being treated must have anatomy that is outside the indications for use for the device used. Statement that anatomy was outside the indications for use would be acceptable as definition of non-standard. If no such statement was present, potential studies should explicitly state anatomical features pertaining to the aneurysm neck, for most devices this

would mean: neck length <10mm, neck angulation of > 60 degrees (angle of intersection between lines of the long axis of the aneurysm and the long axis of the infrarenal neck), and/or neck diameter >32mm within 10mm from the lowest renal artery. Patients would be considered to have a non-standard aneurysm if one or more of the aforementioned criteria were present on preoperative computed tomography (CT) angiography scans. If neither a specific statement about either anatomical criteria or that the patients were “outside IFU” then that study would not be included. If the study combined outcomes for patients with standard and non-standard anatomy that study would only be included if it was possible to analyse the results separately for each study population. If they were grouped together with no specific outcomes reported for non-standard aneurysms, then the study would be excluded

- There must be median (or mean) follow up of at least 1 year to enable meaningful results of short and mid-term data for the studied population
- In order to reduce bias introduced from small case series studies must have at least 50 patients with non-standard anatomy

Exclusion Criteria:

- Studies reporting solely on symptomatic or ruptured aneurysms. If a study includes symptomatic or ruptured aneurysms it is expected that the results for these patients will be identifiable and be able to be excluded from further analysis. If it is not possible to do so then an explicit statement as such will be made in the report to make it clear that this confounding variable exists in the identified study population.
- Previous treatment for abdominal aortic aneurysm

- If the report solely presents on patients treated with an advanced endovascular technique or technology such as fenestrated or branched endovascular repair.
- If the report solely presents treatment of aneurysms utilising the chimney endovascular repair technique or reports of aneurysm treated with endovascular aneurysm sealing technology (EVAS)
- Patients in which adjunctive technology such as endoanchor fixation is used to complement the use of a standard infrarenal stent graft will be excluded
- No statement of aneurysm morphology, either as “outside IFU” or specific anatomic criteria

#### Eligibility Criteria

- Publication dates within 20-year period (1998 – 2018) – to minimise the capturing of reports with physician made endograft devices and prior to widespread acceptance of indication for use anatomical criteria
- English language only results considered
- The population will include all adults with no age restriction

The above protocol was referred to throughout the data identification and extraction phase to ensure it was adhered to.

#### **5.2.2. Definitions and Outcome Criteria.**

Outcome criteria and definitions were based on recommended reporting standards for EVAR, published by the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery [24] and in line with the Pragmatic Minimum Reporting Standards produced for the British Society of Endovascular Therapy (BSET) [99]. Therefore, outcomes within the first 30 days after the index procedure or occurring within the same hospital admission will be reported as perioperative outcomes, those occurring between 30 days and 1 year will be

termed 'Early', those between 1 and 5 years will be termed 'Short', 5 to 10 years will be considered 'Midterm' and > 10 years will be 'Long-term'. Primary outcome measures included perioperative mortality from any cause, all-cause mortality, aneurysm related mortality, reintervention rates and graft related endoleak rates (All type I and III endoleaks). The secondary outcome measures are as follows:

- Primary Technical success
- Clinical success
- Endograft migration
- Visceral vessel patency
- Conversion to open repair
- Length of hospital stay
- Rates of renal dysfunction throughout follow up (the definition used within the given study for renal dysfunction will be used)
- Aneurysm growth throughout follow up (At all time points)

### **5.2.3. Information Sources and Electronic Search Strategy**

An electronic search of the literature was undertaken. The search was applied to MEDLINE (database provider PubMed, from 1998 – 2018) and EMBASE (database provider Ovid, from 1998 to 2018). The search was undertaken once in May 2018. A full record of the search strategy is included within Appendix 1. The full reference list of each full text study assessed was interrogated to identify any relevant articles missed in the original search.

#### 5.2.4. Study Screening and Selection

One reviewer (the chief investigator) reviewed all titles returned from the electronic search and identified those for abstract review. The same reviewer then screened all identified abstracts and excluded those in which the exclusion criteria were fulfilled, or it was clear that the study population did not meet the inclusion criteria. If there was any doubt at this stage the article was selected for full text review. All articles selected for full text review had their reference list cross checked against the initial search and if any were not present then they followed the same screening process as above. This identified a list of articles in which the full text was retrieved or attempted to be retrieved. After review of the full text and frequent reference to the study protocol it was decided whether a study should be included in the systematic review or not. The search strategy results and reasons for exclusion are listed in figure 5.1 below.

Figure 5.1. – Search strategy for Systematic Review of EVAR used outside IFU

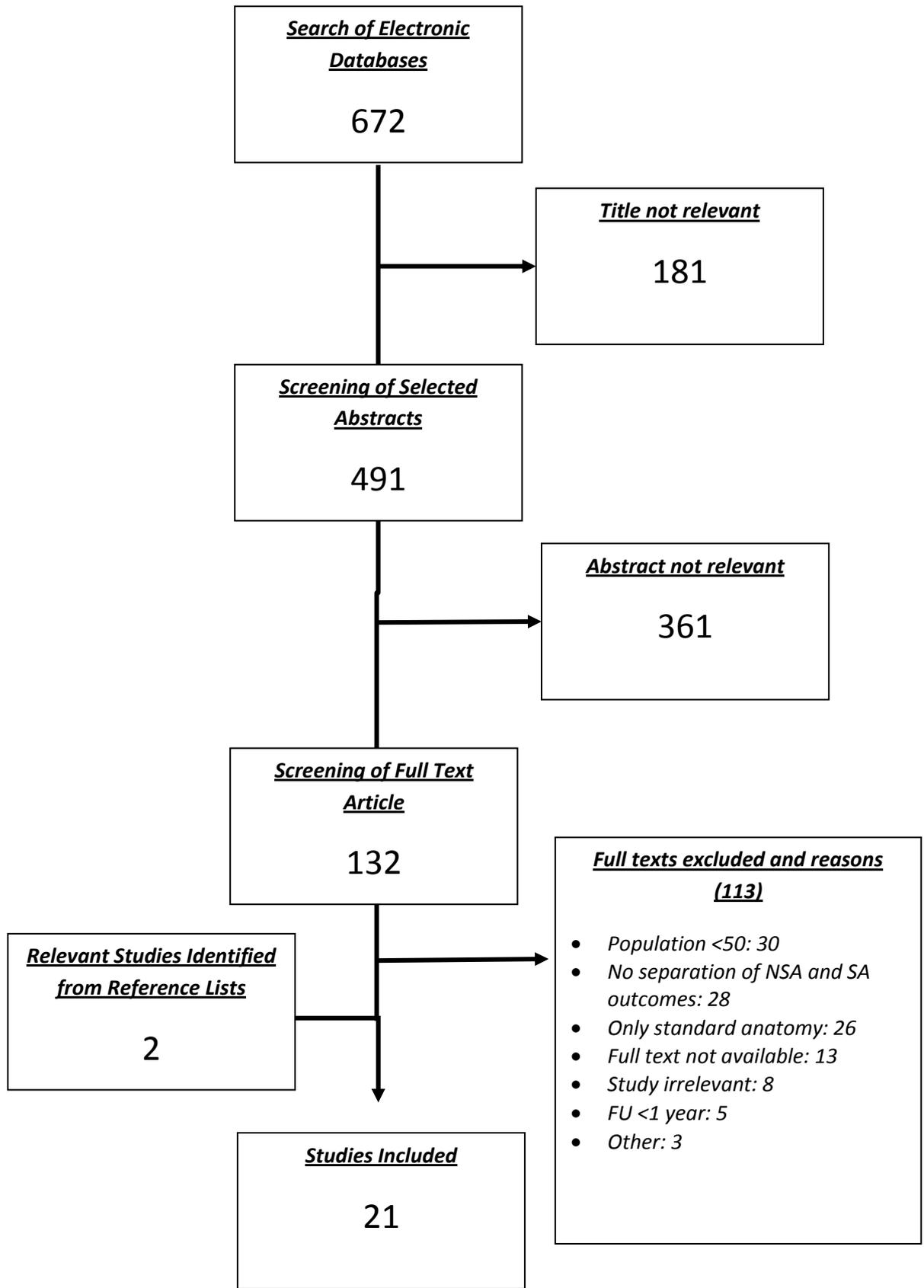


Figure 5.1 - Numbers represent articles. Arrows denote whether articles were excluded or included.

### 5.2.5. Data collection

A data extraction sheet was developed. As well as pertinent information relating to the publication (year of publication, journal etc.) the remaining collected variables were divided in three broad categories: (1) baseline clinical and demographic data, anatomic characteristics, and procedure related characteristics; (2) primary outcome data (3) secondary outcome data, as outlined previously. The methodological quality of the included studies was assessed according to previously described methods – the Methodological Index for Non-Randomized Studies (MINORS) tool was used to assess methodological quality of the included studies. MINORS was developed and designed specifically to assess the quality of non-randomised surgical studies whether comparative or non-comparative. It utilises a 12-item tool, with comparative studies requiring a score for all 12 items and non-comparative studies requiring a score for only the first 8. Each item is given a score for the interrogated study – 0 if it is not reported, 1 if it is reported but inadequate and 2 if it is reported and adequate. The maximum score for non-comparative studies being 16 and 24 for comparative studies. [109]

## 5.3. Results

Of the original 672 titles screened from database searching 21 studies were included in the final analysis. These comprised of 3 non-comparative studies (assessing only the outcomes from NSA) and 18 comparative studies. From all studies the number of patients with SA was 16053 (It was not possible to ascertain the number of SA patients from 3 studies). There were 8458 with NSA analysed across all the studies. The publication dates of the studies ranged from 2003- 2017 and the data collection periods within the studies ranged from 1996 – 2015. One study published in 2001 by Stanley et.al. from Australia [97] was not included but merits mention here. This was the earliest study identified through the search (with a publication limit set to 1998) that details outcomes for more than 50 patients with characteristics of the proximal aortic neck considered to be less than ideal for standard

EVAR. This paper details the early experience of the Australasian team in using the Zenith endovascular stent graft between 1994 - 1998. "Patient selection guidelines" were devised for application to patients during this time, in this region. In relation to the proximal aortic neck, they included:

- Length: 20 mm if straight, 25 mm if angled  $> 15^\circ$  from the longitudinal axis of the suprarenal aorta (either forward or lateral angulation); exclude if angle  $>30^\circ$ .
- Diameter:  $< 28$  mm, uniform (cylindrical), and without filling defects indicating thrombus or soft atheroma; exclude if the diameter progressively increases between the renal arteries and the sac.

These dimensions are like the recognised IFU criteria in use currently but would be considered to fall within IFU guidelines. It is for this reason that this historical report was excluded from further analysis. In fact when the Zenith device gained FDA approval in the U.S.A. in 2003 the IFU guidelines stated at that time were: Neck length  $\geq 15$ mm, neck diameter 18 – 28mm and angulation of  $<60^\circ$ . [98] However, the authors did show with their analysis of 238 patients of whom 128 fell outside their anatomic guidelines certain characteristics that increased the risk of complications during follow up. They showed that the risk of proximal endoleak increased with every millimetre decrease below the 20mm threshold, and that a change in the "contour" of the neck ( $>3$ mm) increased the risk of endoleak. They also showed that migration was positively correlated with a proximal neck diameter of  $>28$ mm. They also revealed that combining adverse neck features lead to an even greater risk of proximal neck complications in an additive manner. In the context of the wider literature this study suggested certain anatomical criteria that would be interrogated later by several studies for different stent grafts and provided important early evidence for adverse clinical outcomes for patients who exhibited more extreme proximal neck anatomy. It appears that these findings went on to influence other studies as the

principle of “contour change” or a localised “bulge” in the proximal aortic neck became a parameter to define hostile aortic neck anatomy in other studies.[110] A variety of stent grafts were investigated in the following studies, they are as follows:

- Excluder and C3 (W. L. Gore & Associates, Flagstaff, AZ, USA)
- Zenith Flex and Zenith Low Profile (Cook Medical, Bloomington, IN, USA)
- Endurant I and II (Medtronic, Inc., Minneapolis, MN, USA)
- AneuRx (Medtronic, Inc., Minneapolis, MN, USA)
- Talent (Medtronic, Inc., Minneapolis, MN, USA)
- Aorfix (Lombard Medical, Oxfordshire, UK)
- Anaconda (Vascutek, Inchinnan, Scotland)
- AFX endovascular system (Endologix, Inc., Irvine, CA, USA),
- Powerlink (Endologix, Inc., Irvine, CA, USA),
- Ancure (Guidant, Menlo Park, CA, USA)
- Vanguard (Boston Scientific, Natick, MA, USA)
- E-Vita (Jotec, Hechingen, Germany)
- Lifepath (Lifesciences, Irvine, CA, USA)
- Fortron (Cordis, Warren, NJ, USA)
- EndoMed EndoFit (LeMaitre Vascular, Burlington, MA, USA)

### **5.3.1. Review of methodology of studies**

Three non-comparative studies were identified and included 4640 patients with NSA.[98, 111, 112] 18 comparative studies including 3818 patients with NSA were identified. [67, 68, 94-96, 103, 106, 110, 113-122]The details of the studies are outlined in table 5.1. and 5.2. below.

**Table 5.1. Details of non-comparative studies for NSA**

<b>Study</b>	<b>Years</b>	<b>No. SA pts</b>	<b>No. NSA pts</b>	<b>MINORS (Max = 16 for NC)</b>	<b>Type of study</b>	<b>Definition of NSA</b>	<b>Stent graft</b>
Pitoulias (NC), 2017[111]	2007 - 2015	88	73	9	Retrospective multicentre cohort study	Utilised IFU of stent graft implanted	Endurant
Gallitto (NC), 2016[112]	2005 - 2010	-	60	8	Retrospective single centre cohort study	Neck length <10mm	Endurant, Zenith
Schanzer (NC), 2011[98]	1999 - 2008	5721	4507	10	Retrospective cohort review from imaging repository	Patients identified from imaging repository and stent grafts used not known for each patient – therefore IFU for available stent grafts on market at time of implantation used to define if patient had NSA	NR

Table 5.1 - NC = Non-comparative, C = Comparative, SA = standard anatomy, NSA = Non-Standard Anatomy, IFU

= Indications for use, NR = Not reported

*Table 5.2. Details of Comparative studies for NSA*

Study	Years	No. SA pts	No. NSA pts	MINORS (Max = 24 for C)	Type of study	Definition of NSA	Stent graft used
<b>Mateo (C), 2016 [113]</b>	2000-2014	178	71	13	Retrospective single centre cohort study	<ul style="list-style-type: none"> <li>• Neck length &lt;15 mm</li> <li>• Neck angulation &gt;60°</li> <li>• &gt;50% circumferential proximal neck thrombus</li> <li>• &gt;50% proximal neck calcification.</li> </ul>	Gore C3, Gore Excluder
<b>Cerini (C), 2016 [95]</b>	2005-2013	94	115	11	Retrospective single centre cohort study	<p><u>“Hostile” neck:</u></p> <ul style="list-style-type: none"> <li>• Neck length &lt;15 mm</li> <li>• Neck angulation &gt;60°</li> <li>• Neck diameter &gt;28mm</li> </ul>	Zenith, Endurant, E-Vita
<b>AbuRahma (C), 2016 [96]</b>	2003-2013	251	275	15	Retrospective single centre cohort study	<p><u>“outside the IFU”</u></p> <ul style="list-style-type: none"> <li>• Neck length &lt;10 mm</li> <li>• Neck angle &gt; 60°</li> <li>• &gt;50% circumferential proximal neck thrombus (&gt;2 mm thick)</li> <li>• &gt;50% calcified proximal neck</li> </ul>	Gore Excluder, Zenith, AneuRx, Endologix, Endurant, Talent

						<ul style="list-style-type: none"> <li>• Reverse taper</li> <li>• Neck diameter &gt; 31 mm</li> </ul>	
<b>Broos (C), 2015 [114]</b>	2009 - 2011	1114	104	16	Retrospective registry dataset (ENGAGE)	Utilised IFU of stent graft used creating 3 groups: REG (regular anatomy), INT (intermediate anatomy but still within IFU), CHA (challenging anatomy – outside of IFU)	Endurant
<b>Walker (C), 2015 [115]</b>	2000-2010	284	205	10	Retrospective multicentre cohort study	Utilised IFU of stent graft implanted	Zenith, Medtronic, AneuRx, Excluder, Talent, Guidant Ancure, Terumo Anaconda
<b>Speziale (C), 2014 [116]</b>	2010-2011	63	133	15	Retrospective multicentre cohort study	“off-L”: Noncylindrical neck Neck angle >65° Neck length <15 mm Neck diameter >28mm	Endurant I, Endurant II, Excluder, Excluder C3, Zenith, Zenith Low

							Profile
<b>Lee (C), 2013 [117]</b>	2004-2007	143	75	16	Retrospective single centre cohort study	Utilised IFU of stent graft implanted	Zenith, Excluder, AneuRx
<b>Antoniou (C), 2013 [118]</b>	NR	0 <sup>a</sup>	60	12	Prospective double centre, non-randomised study	Utilised IFU of stent graft implanted	Zenith, Endurant
<b>Stather (C), 2012 [103]</b>	1999-2010	353	199	17	Retrospective single centre, data collected prospectively	<p><u>"Hostile neck anatomy"</u>:</p> <ul style="list-style-type: none"> <li>• Neck diameter &gt;28 mm</li> <li>• Neck angle &gt;60°</li> <li>• Neck length &lt;15 mm</li> <li>• Neck flare</li> <li>• Neck thrombus.</li> </ul>	Zenith, Talent, Excluder, Endurant, Edwards Lifepath, Endologix Powerlink, Lombard Aorfix, Jotec
<b>Hager (C), 2012 [119]</b>	2002-2009	0 <sup>a</sup>	84	13	Retrospective single centre cohort study	<ul style="list-style-type: none"> <li>• Neck &lt;15mm</li> <li>• <i>Patients excluded if neck angle &gt;60°</i></li> </ul>	Excluder, Zenith
<b>Forbes (C), 2010 [120]</b>	2003-2008	250	68	16	Retrospective single centre cohort study	<ul style="list-style-type: none"> <li>• Neck length &lt;15mm</li> <li>• <i>SA &gt;15mm neck length even if other out of IFU features</i></li> </ul>	Zenith
<b>Chisci (C), 2009 [121]</b>	2005-2007	0 <sup>a</sup>	74	14	Retrospective multicentre	• Neck diameter >28mm	Talent, Zenith

					cohort study	<ul style="list-style-type: none"> <li>• Neck angle &gt;60°</li> <li>• Neck length &lt;15mm</li> <li>• Significant thrombus: (&gt;50% of the proximal neck circumference)</li> <li>• Reverse tapered</li> <li>• Neck bulge: focal neck enlargement &gt;3 mm within 15 mm</li> </ul>	
<b>Abbruzzese (C), 2008 [94]</b>	1999 - 2005	343	222	15	Retrospective single centre cohort study	Utilised IFU of stent graft implanted	Zenith, Gore, Aneurx
<b>Hobo (C), 2007 [67]</b>	1996 - 2006	4031	1152	16	Retrospective analysis of prospective registry data (EUROSTAR)	<ul style="list-style-type: none"> <li>• Neck angle &gt;60° only criterion</li> <li>• <i>All other anatomy SA</i></li> </ul>	Zenith, Talent, Excluder
<b>Choke (C), 2006 [122]</b>	1997 - 2005	87	60	16	Retrospective single centre cohort study	<p><i>“Hostile necks”:</i></p> <ul style="list-style-type: none"> <li>• Neck diameter &gt;28mm</li> <li>• Neck angle &gt;60°</li> <li>• Neck length &lt;10mm</li> <li>• Significant thrombus: (&gt;50% of the proximal neck circumference)</li> <li>• Reverse tapered</li> <li>• Neck bulge: focal</li> </ul>	Talent, Zenith, Excluder, AneuRx, Cordis Fortron, EndoMed EndoFit, Boston Scientific Vanguard,

						neck enlargement >3 mm within 15 mm	Edwards Lifepath
<b>Leurs (C), 2006 [68]</b>	1999- 2005	2872	677	17	Retrospective analysis of prospective registry data (EUROSTAR)	<ul style="list-style-type: none"> <li>• 3 groups analysed:</li> <li>• Neck length &gt;15mm, 10-15, &lt;10mm</li> <li>• <i>All other anatomies considered SA</i></li> </ul>	Talent, Zenith
<b>Fairman (C), 2004 [106]</b>	NR	66	153	10	Retrospective analysis of trial data	<u>“Complicated aortic necks”</u> : <ul style="list-style-type: none"> <li>• Neck length &lt;15mm</li> <li>• Neck diameter &gt;28mm</li> <li>• Neck angulation &gt;45°</li> <li>• Calcified</li> <li>• Thrombus-lined</li> </ul>	Talent LPS
<b>Dillavou (C), 2003 [110]</b>	1999 - 2002	115	91	11	Retrospective single centre cohort study	<u>“Hostile neck anatomy”</u> <ul style="list-style-type: none"> <li>• Neck length &lt;10mm</li> <li>• Neck diameter &gt;26mm</li> <li>• Neck bulge - a focal enlargement of the aneurysm neck of at least 3 mm</li> <li>• Reverse taper</li> </ul>	Ancure

						<ul style="list-style-type: none"> <li>• Neck angle &gt;60°</li> <li>• Significant neck thrombus (&gt;50%)</li> </ul>	
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Table 5.1 - NC = Non-comparative, C = Comparative, SA = standard anatomy, NSA = Non-Standard Anatomy, IFU = Indications for use, NR = Not reported. a= Three studies are included in the comparative analysis as they were comparative in design and methodology but were comparing NSA patients with NSA patients. Anoniou et.al. were comparing the performance of Zenith vs Endurant in NSA, Hager et.al. was comparing the performance of Zenith vs Excluder in NSA and Chisci et.al. were comparing OR, EVAR and fEVAR in NSA.

All but one of the studies identified were retrospective in nature. Most commonly authors would retrospectively analyse data prospectively collected in a database from a single centre. The definition of NSA also varied quite widely between studies. One reason for this was the fact that the studies identified spanned a 20-year period and the indications for use commonly applicable to most stent-grafts has evolved along with technological advancement. As an example, the largest neck diameter that could be treated within IFU with an FDA approved device was 28mm until 2006. In 2006 Cook released a device in which the IFU stated a diameter of 32mm could be treated. As is the nature of competitive market forces, soon after this, other companies began selling devices with IFU stating a neck diameter of 32mm. By 2009 the most commonly used stent grafts were all able to treat a larger diameter. Therefore, earlier studies had used 28mm as a cut off with relation to neck diameter. However, two studies [95, 116] published later and even including patients after 2009 still used the 28mm neck diameter as a cut off for defining NSA. Most studies defined specific anatomic criteria to identify NSA whereas six studies [94, 111, 114, 115, 117, 118] used the stent-graft IFU to define whether a patient met NSA criteria. In addition, one early study [110] used specific anatomical criteria but this essentially mapped directly to the IFU of the only device used within that cohort. Furthermore, with regards to anatomical criteria for inclusion; four studies chose to analyse only one specific anatomical variable [67, 68, 119, 120]. Two of these studies were analyses of the large EUROSTAR

registry with the aim of identifying the specific role that certain neck characteristics play in the clinical outcomes for patients. In the study by Leurs et. al. comparing stent grafts with >15mm, 10 – 15mm and <10mm of neck length the primary aim was never to analyse all NSA and compare with all SA, it was simply to identify the role neck length plays in outcomes after standard endovascular repair, regardless of other features. In that study the group with neck length >15mm is considered the SA group for this and another systematic review [57] however it is important to note that in the SA group 23.1% had “severe aortic neck angulation”. This was significantly less than in the NSA group but is still a significant proportion. This should be borne in mind when analysing and interpreting any results with comparison between NSA and SA groups. For the other three Studies [67, 119, 120] there was simply an unknown proportion of patients with other undesirable anatomical features that were included in the “SA” group (which essentially is the control group for these comparative studies). Therefore, there was this significant confounding factor in these studies that may affect their findings. It must be said that the study by Hager et. al. sought to minimise this somewhat by excluding all patients with severe neck angulation (>60°) from their analysis of patients with and without short necks. In essence there was significant heterogeneity found between studies with regards to definition of the primary defining characteristic of the study populations (NSA). This therefore limits the validity and applicability of any synthesis of results across the studies.

In addition to the above there were other sources of significant heterogeneity within and between studies. The other striking source of heterogeneity is the number of different stent-graft used. This includes some stent-grafts that are no longer available on the market. This is understandable within a systematic review spanning 20 years, but it must also be mentioned that a number of the identified studies included many stent-grafts within the studied population (eight different stent-grafts in one study). In some cases only one

patient received one of the devices. Some reports did adjust and control for this by including only patients treated with one stent graft. And in the case of Leurs et.al., in their analysis of the EUROSTAR registry data, they elected to only include two devices - both with suprarenal fixation as part of their design in an attempt to control for device type as a confounding factor.

In three comparative studies there was no comment on whether there were any conflicts of interest [96, 116, 122] whereas in four others [106, 110, 120, 121] there was clear documentation of conflicts of interest of involved authors. There appeared to be problems in two particular studies with obtaining preoperative imaging in order to perform their analysis meaning that 26% of patients couldn't be included in one study [95] and 71% of the total EVAR cohort in another [115] this of course limits the conclusions that can be drawn from these studies as the studied population cannot be assumed to be representative of the population from which they came.

The non-comparative studies identified were all retrospective in nature and scored adequately using the MINORS tool but consistently failed in similar areas. They all scored poorly in the item related to "prospective collection of data", "unbiased assessment of study endpoint" and "prospective calculation of study size". This is with the exception of the study by Schanzer et. al. in which the reviewers assessing the preoperative anatomy were blinded to the study outcomes. All studies consistently performed well in items relating to "Inclusion of consecutive patients", "Endpoints appropriate to aim of study" and "Loss to follow up less than 5%". The study by Schanzer et.al. provided the vast majority of patients within the non-comparative group and in fact were the largest group of patients contributing overall.

The comparative studies scored inconsistently using the MINORS tool. The mean score of all the included studies was 14 (Range 10 – 17). The maximum available score for a comparative study was 24. There were four areas in which studies consistently scored highly – “A clearly stated aim”, “Inclusion of consecutive patients”, “Loss to follow up <5%” and “Contemporary groups”. In fact, all the studies scored maximum for the latter. There were also two areas which consistently scored poorly – “Unbiased assessment of the study endpoint” and “Prospective calculation of the study size”. With the latter not achieving a single point across all the studies. On all the other criteria there were a range and mix of results. These results from using the MINORS tool highlights the relatively poor methodological quality of the body of evidence identified as outlined above.

### 5.3.2. Demographic information

Demographic information and that on co-morbidities was again inconsistently reported across the studies but some important points should be made about the heterogeneity within studies. See table 5.3.

*Table 5.3. Demographic information from included studies*

Study	Length of FU (months)	NSA age Mean years (+/- SD)	Female NSA population (%)	ASA score	Reporting on comorbidities
Pitoulis (NC), 2017[111]	41	73.4 (8.6)	7.9%	ASA III/IV - 100%	Minimal
Gallitto (NC), 2016[112]	51.4	74.9 (6.2)	12%	ASA III/IV - 100%	Minimal
Schanzer	31	73.9	15.9%	ASA III/IV	NR

<b>(NC), 2011[98]</b>				- 100%	
<b>Mateo (C), 2016 [113]</b>	SA – 30.5 NSA – 38	NR	4.2%	NR	Adequate, no differences
<b>Cerini (C), 2016 [95]</b>	37	75.8 (6.8)	15.7%	NR	Adequate, no differences
<b>AbuRahm a (C), 2016 [96]</b>	30	73.5	20%	NR	NSA > proportion of CHF, CVA/TIA *
<b>Broos (C), 2015 [114]</b>	12	74 (7.7)	20.2%*	ASA III/IV – 50%	NSA > proportion of Cancer diagnosis and “GI complications”*
<b>Walker (C), 2015 [115]</b>	36	74.6 (7)	14.6%*	NR	Adequate, no differences
<b>Speziale (C), 2014 [116]</b>	24	NR	19.6%	ASA III/IV - 85.7%	Adequate, no differences
<b>Lee (C), 2013 [117]</b>	35	74.9	10.7%	NR	Adequate, no differences
<b>Antoniou (C), 2013 [118]</b>	18	74*	Difference between groups*	ASA III/IV – 58%	Adequate, difference in rate of previous CVA*
<b>Stather (C), 2012 [103]</b>	SA – 48.8 NSA – 50.1	73.9 (7.1)	6.5%	ASA higher in NSA	Adequate, no differences
<b>Hager (C), 2012 [119]</b>	18.6	IF 76.6 SF 74.8	No difference between groups	NR	Adequate, no differences
<b>Forbes</b>	51.6	NR	NR	ASA III/IV	Adequate, no

(C), 2010 [120]				– 96.6%	differences
Chisci (C), 2009 [121]	19.5	77.5 (7.0)*	16%	ASA III/IV 88%*	EVAR > proportion of renal insufficiency and CAD
Abbruzzese (C), 2008 [94]	29.6	NR	NR	NR	Adequate, no differences
Hobo (C), 2007 [67]	19.9	72.1 (7.7)*	9.7%*	ASA III/IV 55.0%*	NSA -more often “unfit for open AAA repair and GA”*
Choke (C), 2006 [122]	21.7	74.4 (1.0)	10%	NR	NR
Leurs (C), 2006 [68]	12	73.5	No differences	ASA > III 61.5%*	NSA > proportion of HTN, Renal impairment, Pulmonary disease, "unfit for open or GA"*
Fairman (C), 2004 [106]	21	NR	NR	NR	NR
Dillavou (C), 2003 [110]	18	75.7 *	22%*	NR	Adequate, no differences

Table 5.3. - NC = Non comparative, C = Comparative, SA = standard anatomy, NSA = Non-Standard Anatomy, IFU = Indications for use, NR = Not reported ASA - American Society of Anaesthesiology grading, CAD - coronary artery disease, CHF – Congestive Heart Failure, GA – General Anaesthesia, HTN – Hypertension, IF – Infrarenal fixation, SF – Suprarenal fixation, CVA – Cerebrovascular accident, TIA – Transient Ischaemic Attack.  
\* - Denotes significant variable when compared with comparator group. Length of follow up is reported as in included study whether that be mean or median follow up.

Across all the studies the mean age of the patients was relatively similar with all reporting within the range of 72.1 – 77.5 years for NSA patients. The groups were also relatively homogenous within studies as only two [67, 110] found a statistical difference in the age between groups. One [110] found the NSA cohort were older and the other [67] found that the SA group were older. Antoniou et.al. reported a difference in the age of the two populations being studied but these were both NSA populations as that study was comparing two different types of stent graft. Similarly, Chisci et. al. found a difference in the age between their three NSA groups of OR, EVAR and fEVAR. In all cases the difference between the means was less than 3 years. With regards to gender within and across studies there is significant heterogeneity and it is not clear exactly why this may be the case. It is suggested that women tend to present with more severe anatomy of their AAA by nature [102] and this would explain heterogeneity within studies to an extent but there doesn't appear to be a clear explanation why there should be such a large difference between studies. The proportion of women with NSA undergoing EVAR across the studies ranges from 4.2 – 22%. With regards to other medical conditions and co-morbidities the studies overall were reasonable at least in reporting the proportions of patients with basic vascular risk factors such as hypertension, coronary artery disease, diabetes etc. however studies often did not report the ASA grade. There were 10 studies in total not reporting ASA grade of patients. The ASA grade is simplistic and by no means a perfect assessment of a patient's fitness for surgery but it is a standard preoperative variable usually readily available and therefore should be included in any report and indeed is recommended in the minimum reporting standards for endovascular repair as a necessary addition to any data set [99]. In those that did report ASA grade it was usually reported as a proportion of patients with ASA grade 3 or above, and this proportion ranged from 50 – 100% across the studies. Clearly there is significant heterogeneity between different studies with regards to ASA

grade. In three studies [67, 68, 103] patients with NSA were found to have a statistically significant higher ASA grade than their SA counterparts. In the EUROSTAR studies by Leurs et.al and Hobo et. al. patients were also noted to be more comorbid and “*unfit for open repair or general anaesthesia*” with an increased rate of renal and pulmonary pre-existing conditions. In another study by Broos et. al. the NSA group had a higher prevalence of cancer at baseline, and in AbuRahma et.al. study NSA patients were significantly more likely to suffer with congestive heart failure and previous stroke. This narrative analysis of demographics and reported comorbidities for included studies shows that there is significant heterogeneity between studies and within studies for important baseline characteristics and that the reporting of comorbidities is imperfect, and reporting of ASA grade is often non-existent. However, from the limited data available it does seem to suggest, that the NSA patients have a higher ASA score, more comorbidities and are less “fit” than their SA counterparts preoperatively. This is an important confounding factor for many of these studies with regards to the validity and applicability of clinical outcome results especially with regards to mortality and complication rates.

One other important point of note is that the studies inconsistently dealt with varying presentation of AAA. Some explicitly stated that only elective patients were included in their cohort, others expressly stated that emergent or symptomatic patients were included [95, 114] and in others there was simply no mention.

### **5.3.3. Anatomical data**

What was clear from the included studies’ reports was that anatomical characteristics are inconsistently reported. Often the pertinent anatomical characteristics (i.e. for the proximal aortic neck) were reported either as a mean value with standard deviation for the whole NSA group or proportions of patients violating a stated anatomical criterion were given (i.e. X% had a neck length <10mm). When only the mean values are reported this can often be

misleading as the mean value for any given characteristic is often well within IFU anatomical criteria due to the fact that patients vary in their nature in the breach of the IFU and therefore for any given single characteristic a large proportion of patients would be well within IFU criteria. If and when a mean anatomical variable fell outside the IFU criteria it was usually because that particular study was simply assessing one IFU criteria (e.g. neck length only). The pertinent anatomical characteristics reported for each study are detailed in the tables below. (see tables 5.4 – 5.7): Data are presented as mean (+/- S.D. or proportion) or Median (Range or IQR), when this information was available from the study

**Table 5.4. Anatomical data (AAA diameter) for included studies**

<b>Study</b>	<b>SA AAA Diameter mean +/- S.D or median (IQR), (mm)</b>	<b>NSA AAA Diameter mean +/- S.D or median (IQR), (mm)</b>	<b>Significant difference between groups</b>
<b>Pitoulis (NC), 2017[111]</b>	-	NS	-
<b>Gallitto (NC), 2016[112]</b>	-	60.4 +/- 12.2	-
<b>Schanzer (NC), 2011[98]</b>	-	54.8mm (59% <55mm)	-
<b>Mateo (C), 2016 [113]</b>	56 (34–112)	59 (40–100)	NS
<b>Cerini (C), 2016 [95]</b>	59.9 +/- 1.2	62.4 +/- 0.9	NS
<b>AbuRahma (C), 2016 [96]</b>	NR	NR	-
<b>Broos (C), 2015 [114]<sup>a</sup></b>	REG – 58 (53 – 64)	CHA - 61 (55-73)	<0.01
<b>Walker (C), 2015 [115]</b>	5.7 +/- 0.9	60 +/- 12	<0.001
<b>Speziale (C), 2014</b>	60.2 ± 12.7	61.9 ± 10.9	NS

[116]			
Lee (C), 2013 [117]	56.9	61.5	0.002
Antoniou (C), 2013 [118] <sup>b</sup>	-	ZEN - 67 +/- 11 END - 63 +/- 15	NS
Stather (C), 2012 [103]	64.8 +/- 12.0	64.2 +/- 9.7	NS
Hager (C), 2012 [119] <sup>c</sup>	-	IF - 58 (34 - 80) SF - 49 (48 - 82)	NS
Forbes (C), 2010 [120]	NR	NR	-
Chisci (C), 2009 [121]	-	62 (50 - 110)	NS
Abbruzzese (C), 2008 [94]	54.5 +/- 9.3	57.3 +/- 11.9	< .001
Hobo (C), 2007 [67]	57.9 +/- 10.4	63.8 +/- 12.6	<0.0001
Choke (C), 2006 [122]	62.7 +/- 1.1	65.3 +/- 2.0	NS
Leurs (C), 2006 [68] <sup>d</sup>	A = 61.3 +/- 10.7	B = 62.2 +/- 11.3 C = 62.9 +/- 11	< 0.0314
Fairman (C), 2004 [106]	NR	NR	
Dillavou (C), 2003 [110]	53.8	54.8	NS

Table 5.4. IQR – Interquartile range, SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported a - Broos et al. compared three groups of patients, REG vs INT vs CHA, they represent three 'levels' of anatomical complexity. CHA represents out of IFU for the device used and the other two represent in the IFU. Data presented are the comparison between the REG and CHA group. b – Antoniou et. al. compared two groups both with NSA – those receiving Zenith device (ZEN) and those receiving Endurant (END) device. C – Hager et.al. Compared two groups both with NSA – those receiving Excluder infrarenal fixation device (IF) and those receiving Zenith suprarenal fixation device (SF). D – Leurs et.al. compared three groups with different neck lengths, (A) – >15mm, (B) – 10 – 15mm, (C) - <10mm.

Across the studies twelve provide an average diameter for SA and twenty provide a diameter for NSA aneurysms. The median and range of these combined values are 58mm (53.8 – 64.8) for SA AAA. For NSA AAA it is 61.7mm (49 – 67). In three studies [98, 110, 119] the average AAA diameter in NSA was less than 55mm. In fact, across the studies there was a significant proportion of patients treated with aneurysms <55mm. The paper by Schanzer et.al. documents that 59% of the aneurysms treated in that large 10228 patient cohort had small AAA <55mm. In total across all the studies at least 6347 (25.9%) had aneurysms <55mm treated and included in the studies. The actual number is higher than this because some studies did not report the proportion of patients treated <55mm. There is therefore wide variation between studies with regard to the selection and size criteria for who undergoes AAA repair. Six of the 18 comparative studies found that the NSA patients had a significantly larger AAA preoperatively than their SA counterparts [67, 68, 94, 114, 115, 117].

To continue the examination of the anatomical findings from the papers see table 5.5. below for details of the reported neck lengths from the various included studies.

**Table 5.5. Anatomical data (Neck Length) for included studies**

<b>Study</b>	<b>SA Neck Length, mean +/- S.D or median (IQR), (mm)</b>	<b>NSA Neck Length, mean +/- S.D or median (IQR), (mm)</b>	<b>Significant difference between groups</b>
<b>Pitoulas (NC), 2017[111]</b>	-	NR	-
<b>Gallitto (NC), 2016[112]</b>	-	8.4 +/- 1.6	-
<b>Schanzer (NC), 2011[98]</b>	-	20.7 +/- 12.7 (18% 10 - 15mm, 24% <10mm)	-
<b>Mateo (C), 2016 [113]</b>	22 (12–65)	15 (10–40) (78.9% <15mm)	< 0.001
<b>Cerini (C), 2016 [95]</b>	27.3 (15 - 45)	10.2 (5 - 14) (34.4% <10mm)	< 0.05
<b>AbuRahma (C), 2016 [96]</b>	NR	(13% <10mm)	-
<b>Broos (C), 2015 [114]<sup>a</sup></b>	29 +/- 11	22 +/- 15	< 0.01
<b>Walker (C), 2015 [115]</b>	26.5 (20.7-35.0)	9.9 (6 - 13.9)	< 0.001
<b>Speziale (C), 2014 [116]</b>	24.9 ± 7.5	14.4 ± 6.7	< 0.001
<b>Lee (C), 2013 [117]</b>	25	13 (30.7% <10mm)	< 0.001
<b>Antoniou (C), 2013 [118]<sup>b</sup></b>	-	ZEN: 20 +/- 13 (63% <15mm) END: 18 +/- 10 (52% <15mm)	NS
<b>Stather (C), 2012 [103]</b>	NR	NR	NS
<b>Hager (C), 2012</b>	-	IF - 12 (7-14)	NS

[119] <sup>c</sup>		SF - 11 (5-14)	
Forbes (C), 2010 [120]	NR	NR	-
Chisci (C), 2009 [121]	-	10 (8 - 12)	Significant difference between groups - significantly more <10mm necks in fEVAR
Abbruzzese (C), 2008 [94]	27 +/- 10.7	22.2 +/- 11.9 (39% oIFU)	< 0.001
Hobo (C), 2007 [67]	27.6 +/- 12.3	24.8 +/- 10.4	< 0.0001
Choke (C), 2006 [122]	29.4 +/- 1.6	22.6 +/- 1.9	< 0.0075
Leurs (C), 2006 [68]	NR	NR	
Fairman (C), 2004 [106]	NR	NR	
Dillavou (C), 2003 [110]	21.8	14.4	< 0.001

Table 5.5. IQR – Interquartile range, SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported a - Broos et al. compared three groups of patients, REG vs INT vs CHA, they represent three 'levels' of anatomical complexity. CHA represents out of IFU for the device used and the other two represent in the IFU. Data presented are the comparison between the REG and CHA group. b – Antoniou et. al. compared two groups both with NSA – those receiving Zenith device (ZEN) and those receiving Endurant (END) device. C – Hager et.al. Compared two groups both with NSA – those receiving Excluder infrarenal fixation device (IF) and those receiving Zenith suprarenal fixation device (SF)

Unsurprisingly many studies report a statistically significant difference between NSA and SA patients for neck length given this is one of the primary neck characteristics that defines NSA. It is important to note however that in some studies [67, 94, 114] the neck lengths for the NSA groups fall well within IFU criteria (>20mm) and highlight the potential for misleading reporting if average values alone are used to define certain neck characteristics.

In fact, in the case of Abbruzzese et.al. all the primary neck characteristics are within IFU criteria when presented as means. Helpfully this report also documents the proportion of patients falling out with each IFU criteria to give a full understanding of the anatomy that is being investigated. For details on neck diameter in the included studies see table 5.6. below.

**Table 5.6. Anatomical data (Neck Diameter) for included studies**

Study	SA Neck Diameter, mean +/- S.D or median (IQR), (mm)	NSA Neck Diameter, mean +/- S.D or median (IQR), (mm)	Significant difference between groups
Pitoulis (NC), 2017[111]	-	NS	
Gallitto (NC), 2016[112]	-	23.5 +/- 3	
Schanzer (NC), 2011[98]	-	23.1 +/- 3.1 (91% <28mm)	
Mateo (C), 2016 [113]	23.7 (18.5–31.5)	23 (18–29)	NS
Cerini (C), 2016 [95]	24.3 +/- 1.2	25.6 +/- 0.8	NS
AbuRahma (C), 2016 [96]	-	(6% >31mm)	-
Broos (C), 2015 [114] <sup>a</sup>	24 +/- 4	24 +/- 4	NS
Walker (C), 2015 [115]	24.5 (22.5-26.7)	23.5 (21.5-25.9)	< 0.01
Speziale (C), 2014 [116]	22.5 ± 2.9	23.4 ± 2.5	0.0029
Lee (C), 2013 [117]	(>28 mm - 4.9%)	(>28 mm - 12.0%)	NS
Antoniou (C), 2013 [118] <sup>b</sup>	-	ZEN 24 +/- 3 END 26 +/- 4	NS
Stather (C), 2012 [103]	NR	NR	NS
Hager (C), 2012 [119] <sup>c</sup>	NR	NR	-
Forbes (C), 2010 [120]	NR	NR	-
Chisci (C), 2009 [121]		(>28mm - 74%)	Significant

			difference between groups – Larger diameter in EVAR and fEVAR vs OR
<b>Abbruzzese (C), 2008 [94]</b>	22.7 +/- 2.3	23.7 +/- 2.7 (18% oIFU)	< 0.001
<b>Hobo (C), 2007 [67]</b>	24.2 +/- 3.3	24.2 +/- 3.2	NS
<b>Choke (C), 2006 [122]</b>	23.3 +/- 0.3	26.3 +/- 0.5	< 0.0001
<b>Leurs (C), 2006 [68]<sup>d</sup></b>	A = 24.6 +/- 3.4	B = 24.8 +/- 3.3 C = 25.7 +/- 3.6	< 0.0004
<b>Fairman (C), 2004 [106]</b>	NR	NR	
<b>Dillavou (C), 2003 [110]</b>	NR	NR but all <26	

Table 5.6 - IQR – Interquartile range, SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported a - Broos et al. compared three groups of patients, REG vs INT vs CHA, they represent three 'levels' of anatomical complexity. CHA represents out of IFU for the device used and the other two represent in the IFU. Data presented are the comparison between the REG and CHA group. b – Antoniou et. al. compared two groups both with NSA – those receiving Zenith device (ZEN) and those receiving Endurant (END) device. C – Hager et.al. Compared two groups both with NSA – those receiving Excluder infrarenal fixation device (IF) and those receiving Zenith suprarenal fixation device (SF). D – Leurs et.al. compared three groups with different neck lengths, (A) – >15mm, (B) – 10 – 15mm, (C) - <10mm.

As stated earlier there were significant differences in the definition of what constituted a large diameter neck that defined NSA. Furthermore, there were often no details on exactly how the neck was measured on preoperative imaging and when there was - the method of measurement was inconsistent. Gallito et. al. report that the neck was measured from the most caudal renal artery to the beginning of the aneurysm from adventitia to adventitia for

every millimetre but no comment on how the final value of neck diameter was decided from these measurements. Gallitto et. al. comment that they only measured neck diameter at the level of the lowest renal artery. Therefore, there is significant disparity between studies as to how anatomical measurements are made. The table below details the results for neck angulation.

**Table 5.7. Anatomical data (Neck Angulation) for included studies**

Study	SA Neck Angulation, mean +/- S.D or median (IQR), (°)	NSA Neck Angulation, mean +/- S.D or median (IQR), (°)	Significant difference between groups
Pitoulis (NC), 2017[111]	-	NS	-
Gallitto (NC), 2016[112]	-	Alpha angle >45° 10%, Beta angle >60° 33% A and B angle 10%	-
Schanzer (NC), 2011[98]	-	36.9 (15.4) (8% >60°)	-
Mateo (C), 2016 [113]	29.7	41.8 (23.9% >60°)	0.04
Cerini (C), 2016 [95]	-	11.1% >60°	-
AbuRahma (C), 2016 [96]	-	18% >60°	-
Broos (C), 2015 [114] <sup>a</sup>	Alpha – 15 +/- 14 Beta – 24 +/- 18	Alpha - 45+/-29 Beta - 68+/-29	< 0.01 < 0.01
Walker (C), 2015 [115]	35.5 (26.4-44.2)	43.3 (31.8-55.5)	< 0.001
Speziale (C), 2014 [116]	22.1 ± 14.5	32 ± 19.8	< 0.001
Lee (C), 2013 [117]	>60° - 0.7%	>60° - 68%	< 0.001
Antoniou (C), 2013 [118] <sup>b</sup>	-	ZEN 56+/- 20 (59% >60°) END 61+/- 25 (67% >60°)	NS
Stather (C), 2012 [103]	NR	NR	-

<b>Hager (C), 2012 [119]</b>	NR	NR	-
<b>Forbes (C), 2010 [120]</b>	NR	NR	-
<b>Chisci (C), 2009 [121]</b>	-	>60°: 53%	-
<b>Abbruzzese (C), 2008 [94]</b>	Alpha 16.3 +/-15.3  Beta: 34.6 +/- 17.6	Alpha - 29.2 +/- 21.8 (26% oIFU)  Beta: 46.7 +/- 20.7 (14.7% oIFU)	< 0.001  < 0.001
<b>Hobo (C), 2007 [67]</b>	>60°: 0%	>60°: 100%	
<b>Choke (C), 2006 [122]</b>	27.5 +/- 1.8	45.9 +/- 3.1	< 0.0001
<b>Leurs (C), 2006 [68]<sup>d</sup></b>	A = 23.1% (>60°)	B = 28.7% (>60°) C = 28.1% (>60°)	0.0127
<b>Fairman (C), 2004 [106]</b>	NR	NR	
<b>Dillavou (C), 2003 [110]</b>	22	40	< 0.001

Table 5.7 - IQR – Interquartile range, SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported a - Broos et al. compared three groups of patients, REG vs INT vs CHA, they represent three 'levels' of anatomical complexity. CHA represents out of IFU for the device used and the other two represent in the IFU. Data presented are the comparison between the REG and CHA group. b – Antoniou et. al. compared two groups both with NSA – those receiving Zenith device (ZEN) and those receiving Endurant (END) device. C – Hager et.al. Compared two groups both with NSA – those receiving Excluder infra renal fixation device (IF) and those receiving Zenith suprarenal fixation device (SF). D – Leurs et.al. compared three groups with different neck lengths, (A) – >15mm, (B) – 10 – 15mm, (C) - <10mm.

Again, there is significant discordance between the studies with how angulation is both reported and measured. Few studies comment on both alpha and beta angulation. Most concern their reports only with Beta angulation. The majority of studies do show a significant difference between SA and NSA groups in terms of neck angulation. With those in the NSA group exhibiting higher mean or median neck angulation. The values, however, were rarely outside the IFU for neck angulation (principally 60 degrees) with the notable exception of the study by Hobo et. al. in which neck angulation was the primary characteristic under scrutiny.

## 5.4. Primary Outcome Results

The primary outcome data as stated in the protocol are: perioperative mortality from any cause, all-cause mortality, aneurysm related mortality, reintervention rates and graft related endoleak rates (All type I and III endoleaks).

### 5.4.1. Perioperative Mortality

The following table documents the perioperative mortality rates reported in the comparative studies. The three non-comparative studies could not be included in analysis of perioperative mortality for the following reasons: In one of the non-comparative studies mortality rate was given for the whole EVAR population and it was not possible to discern it for the NSA group. In the other two non-comparative studies the perioperative mortality was not reported. Those studies contributed 4640 patients to the total NSA cohort of 8458 and 5809 patients to the total SA cohort of 16053. There were three comparative studies which did not report the perioperative mortality rate and have not been included in the following table [106, 115, 119] (Contributing 442 NSA patients and 350 SA patients). One study [120] only reported perioperative mortality for the entire EVAR cohort and didn't define that of the NSA cohort and therefore were excluded from the following analysis (Contributing 68 NSA patients and 250 SA patients) Two further comparative studies that only examined patients with NSA having different treatment options were excluded from the below analysis because there was no SA cohort for comparison, the perioperative mortality rate in those studies for NSA patients undergoing standard EVAR was 1.3% [121] and 4% [118] (Contributed 134 patients to NSA total).

*Table 5.8. Perioperative mortality for SA and NSA patients*

Study	N	SA Perioperative Mortality, n (%)	N	NSA Perioperative Mortality, n (%)	Significant difference between groups
Mateo (C), 2016	178	0	71	0	
Cerini (C), 2016	94	0 (6.3% - all emergency)	115	0 (7.8% - all emergency)	NS
AbuRahma (C), 2016	251	1 (0.4%)	275	4 (1.5%)	NS
Broos (C), 2015 a	1114	13 (1.2%)	104	3 (2.9%)	NS
Speziale (C), 2014	63	0	133	4 (3%)	NS
Lee (C), 2013	143	3 (2.1%)	75	0	NS
Stather (C), 2012	353	4 (1.1%)	199	1 (0.5%)	NS
Abbruzzese (C), 2008	343	6 (1.7%)	222	4 (1.8%)	NS
Hobo (C), 2007	4031	117 (2.9%)	1152	46 (4.0%)	NS
Choke (C), 2006	87	5 (6%)	60	2(3%)	NS

<b>Leurs (C), 2006 A = Neck length &gt;15mm B = Neck length 10- 15mm C = Neck length &lt;10mm</b>	2872	A = 72 (2.6%)	677	B = 24 (5.0%) C = 8 (4.2%)	B vs A SIG OR and CI 1.77 (1.08–2.87)
<b>Dillavou (C), 2003</b>	115	0	91	1 (1.1%)	NS
<b>Total</b>	9644	221 (2.3%)	3174	97 (3.1%)	

Table 5.8. SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported.

After exclusions of studies for the above reasons 9644 SA patients of a total of 16053 (60%) and 3174 of 8458 NSA patients (37.5%) were available to analyse perioperative mortality rates. It should be commented that in the study by Cerini et.al. their reported perioperative mortality rate included patients treated with a ruptured AAA. No patients treated electively in their series died perioperatively and therefore for the purposes of this analysis the perioperative mortality rate in that study was deemed to be 0%. Only one study reported a significant difference in perioperative mortality between the groups [68]. This was a large EUROSTAR registry study investigating the effect of neck length on clinical outcomes, they compared three groups of patients; Neck length >15mm (A), 10 – 15mm (B) and <10mm (C). Interestingly there was a significant difference in mortality rates when group B was compared with group A (5% vs 2.6% respectively, OR 1.7 95% CI 1.08 – 2.87) but, importantly not when group A was compared with the more severe <10mm neck length group C. The authors offered no explanation as to this disparity but on review of the

preoperative characteristics the groups were similar. In most cases group B had characteristics that were an intermediate between groups A and C as one would expect. Indeed, in the calculation of the odds ratio the authors *“Adjusted for ASA class >3, hypertension, renal and pulmonary impairment, unfitness for open surgery or anaesthesia, maximal aneurysm diameter, infrarenal neck diameter, angulation, and team experience”*. There were significantly more patients with significant beta angulation within group B compared to group C however – 28.7% vs 28.1% respectively. Whether this contributed to the outcomes seen is difficult to ascertain, though seems unlikely. The remaining studies showed no difference between SA and NSA for perioperative mortality rates with a range for SA patients from 0 – 6% with the combined total mortality rate being 2.3%. For NSA patients the range was 0 – 5% with a combined total rate of 3.1%.

#### **5.4.2. Aneurysm Related Mortality**

The aneurysm related mortality for the included studies where available is presented in the table below (See table 5.9.). One non comparative study [98] did not report aneurysm related mortality – with that study contributing 5721 SA patients (35.6% of total SA patients) and 4507 NSA patients (53.3% of total SA patients). That study was purely an imaging repository-based study and therefore could not comment on clinical outcomes such as mortality. It should therefore be highlighted that a large proportion of the populations being studied that have been published have no available clinical outcome data. Any interpretation of results presented within this review must bear this in mind. In addition to the above mentioned study there were 4 further, comparative, studies that did not report aneurysm related mortality over the long term follow up [96, 106, 110, 122] they contributed together 519 (3.2%) of SA patients and 579 (6.8%) of NSA patients. In one study [96] it was reported that only one patient died of aneurysm rupture during follow up of a total cohort of 526 patients treated but it does not report from which group this

patient was in and does not mention aneurysm related mortality. Therefore, it has been excluded from further analysis with respect to aneurysm related mortality.

*Table 5.9. Aneurysm Related Mortality for SA and NSA patients*

Study	Length of FU, mean or median (Months)	N	SA Aneurysm Related Mortality, n(%)	N	NSA Aneurysm Related Mortality, n(%)	Significant difference between groups
Pitoulis (NC), 2017[111]	41	88	-	73	0	N/A
Gallitto (NC), 2016[112]	51.4	-	-	60	2 (3%)	N/A
Mateo (C), 2016 [113]	SA – 30.5 NSA – 38	178	0	71	0	NS
Cerini (C), 2016 [95]	37	94	0	115	0	NS
Broos (C), 2015 [114]	12	1114	15 (1.3%)	104	3 (2.9%)	NS
Walker (C), 2015 [115]	36	284	8 (2.8%)	205	2 (1%)	NS
Speziale (C), 2014 [116]	24	63	0	133	0	NS
Lee (C), 2013 [117]	35	143	1 (0.7%)	75	1 (1.3%)	NS
Antoniou (C), 2013 [118]	18	-	-	60	1 (1.7%)	NS
Stather (C), 2012 [103]	SA – 48.8 NSA – 50.1	353	6 (1.7%)	199	4 (2.0%)	NS
Hager (C), 2012 [119]	18.6	-	-	84	0	NS

<b>Forbes (C), 2010 [120]</b>	51.6	250	0	68	0	NS
<b>Chisci (C), 2009 [121]</b>	19.5	0	-	74	3 (4.1%)	NS
<b>Abbruzzese (C), 2008 [94]<sup>a</sup></b>	29.6	343	Freedom from ARM: 1 year – 100% 5 years - 100%	222	Freedom from ARM: 1 year – 94% 5 years - 89%	< 0.001
<b>Hobo (C), 2007 [67]</b>	19.9	4031	190 (4.7%)	1152	78 (6.8%)	NS
<b>Leurs (C), 2006 [68]<sup>b</sup></b>	12	2872	A = 15 (2%)	677	B = 4 (1.9%) C = 0	NS

Table 5.9. SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported, ARM – Aneurysm related mortality. a - Freedom from aneurysm related mortality presented within study by Kaplan-Meier analysis. b – Leurs et.al. compared three groups with different neck lengths, (A) – >15mm, (B) – 10 – 15mm, (C) - <10mm.

The length of follow up within studies ranged from 12 months to 51.6 months. Most commonly the median follow up time was reported but occasionally mean follow up time was documented. For the majority of studies, the number of aneurysm related deaths were reported, and this was simply reported as a proportion of the total patient population to give the above quoted figures for aneurysm related mortality across the follow up. In one study [94] as mentioned in the table above Kaplan Meier freedom from aneurysm related mortality was considered and compared between the groups. It was in this study where there was a significant difference both at 1 year and 5-year estimates of freedom from aneurysm related mortality. The difference was 100% freedom in SA patients at both time points and 94% and 89% at 1 and 5 years respectively for NSA patients. In total aneurysm related mortality was attributed to 14 deaths (2.5% of total population of 565). Ten of

these deaths occurred during the index hospital admission and 3 of the remaining four “late” deaths were secondary to aneurysm rupture. It should be noted that in this study no deaths in the SA group were reported as aneurysm related however there were 6 perioperative deaths in the SA group and in line published reporting standards [24] [99] and other published studies these would normally be considered as aneurysm related mortality. This point highlights the disparity in the reporting of aneurysm related mortality figures within the literature. Taking this into account the aneurysm related mortality ranged from 0 to 4.7%, for SA patients, in the included studies. For NSA patients the aneurysm related mortality ranged from 0 to 6.8% for those included studies presenting figures as proportions of the total population.

#### **5.4.3. All-cause mortality**

There were six studies that did not report all-cause mortality through follow up. These include the previously mentioned large non-comparative study [98] and five comparative studies [94, 119-122]. Together they comprise 6401 SA patients (39.9% of total SA cohort and 5015 NSA patients (59.3% of total NSA cohort). Of the 15 studies with data available for analysis regarding all-cause mortality through the follow up 6 report an average follow up time of less than 2 years and 9 report more than 2 years follow up. These groups are presented together in the two tables below (Table 5.10. and 5.11.)

**Table 5.10. – All cause mortality for studies reporting follow up <2 years**

Study	Length of FU, mean or median (Months)	N	SA pts - All cause mortality over FU	N	NSA pts - All cause mortality over FU	Significant difference between groups
Broos (C), 2015 [114]	12	1114	7.2%	104	9.6%	NS
Antoniou (C), 2013 [118]	18	-		60	9 (15%)	NS
Hobo (C), 2007 [67]	19.9	4031	23.6%	1152	24.1%	NS
Leurs (C), 2006 [68] <sup>a</sup>	12	2872	A = 19.2%	677	B = 20.2% C = 34.0%	NS
Fairman (C), 2004 [106]	21	66	2 yrs:81.7%	153	2 yrs.: 84.3%	NS
Dillavou (C), 2003 [110]	18	115	5.2%	91	4.4%	NS

Table 5.10. . SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported, ARM – Aneurysm related mortality. a – Leurs et.al. compared three groups with different neck lengths, (A) – >15mm, (B) – 10 – 15mm, (C) - <10mm.

In the above studies with an average follow up period ranging from 12 – 21 months the all-cause mortality at that follow up point ranged between 5.2 – 23.6% for SA patients and 4.4 – 34% for NSA patients. In no instance was there a significant difference between SA and NSA groups at this follow up time point. The following table documents the outcomes in studies with a follow up period longer than 2 years (See table 5.11.)

*Table 5.11. – All cause mortality for studies reporting follow up >2 years*

Study	Length of FU, mean or median (Months)	N	SA pts - All cause mortality over FU	N	NSA pts - All cause mortality over FU	Significant difference between groups
Pitoulas (NC), 2017[111]	41	88	-	73	21.1%	N/A
Gallitto (NC), 2016[112]	51.4	-	-	60	1 year - 3% 3 years - 13% 5 years - 30%	N/A
Mateo (C), 2016 [113]	SA - 30.5 NSA – 38	178	2 years: 7.7%	71	2 years: 6.6%	NS
Cerini (C), 2016 [95]	37	94	22.8%	115	24.4%	NS
AbuRahma (C), 2016 [96]	30	251	6.3%	275	13.4%	0.008
Walker (C), 2015 [115]	36	284	21.1%	205	21.5%	NS
Speziale (C), 2014 [116]	24	63	3.2%	133	5.4%	NS
Lee (C), 2013 [117]	35	143	Survival: 1 yr. 90.7% 2 yr. 84.6% 3 yr. 79.9%	75	Survival: 1 yr. 92.5% 2 yr. 86.3% 3 yr. 71.5%	NS

<b>Stather (C), 2012 [103]</b>	SA – 48.8 NSA – 50.1	353	5-year mortality: 15.1%	199	5 yr. mortality: 14.6%	NS
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Table 5.11. . SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported, ARM – Aneurysm related mortality.

As can be seen from the table above there was only one study where there was a significant difference in all-cause mortality between the two groups during long term follow up [96]. The authors comment that only one death was secondary to aneurysm rupture, but that study also found an increased rate of early reintervention, as well as early and late type 1 endoleak for NSA patients. There did not appear to be any other explanation for the higher mortality rate in the NSA group. There were two studies with sufficiently long enough follow up that survival rates could be commented on out to 5 years – in one [112] the five year survival rate was 70% (In NSA patients) and in the other [103] it was 85.4% (for NSA patients), and 84.9% for SA patients.

#### 5.4.4. Reintervention Rates

Of all the included studies there were three that showed a statistically significant difference in reintervention rates. [67, 96, 103]. The first study by AbuRahma et.al. who investigated a relatively large cohort of patients – 526 in total, which make up 2.2% of the total population of included studies. In that study the authors found that the rate of reintervention within 30 days was statistically significant between groups with 10% of SA patients requiring a reintervention and 24% of NSA patients requiring a reintervention ( $p < 0.0001$ ). The authors noted significantly more early (<30 day) type 1 endoleaks in the NSA group compared with the SA group. It should also be noted that there were a large number of type 1a endoleaks noted in the NSA group within 30 days compared to other studies. They report 18% of NSA patients had a type 1a endoleak within 30 days when the range from other studies was 0 – 10.9%. The authors define “early” endoleak as “a leak detected intraoperatively, or less than 30 days postoperatively”. They do not specify whether their

rate includes those patients in whom a type 1a endoleak was detected intraoperatively and sealed utilising an adjunctive manoeuvre. Unfortunately they do not report technical success rates, which in line with the reporting standards [24], would help the reader to determine whether the above point is true. Furthermore, the vast majority of all interventions performed within 30 days for both groups were either a proximal cuff extension or proximal aortic stent (97%). There were significantly more proximal cuff extensions in the NSA group vs SA group (16% vs 5% respectively,  $p = 0.0001$ ), presumably secondary to the higher rate of type 1 endoleak primarily, again it is not defined within the study whether these were intraoperative adjunctive procedures or secondary procedures on another day from the index procedure. That study also found that through multivariate analysis beta angulation of  $> 60$  degrees and neck length of  $<10$ mm were predictive factors for early intervention. The study found no significant difference in late reintervention rates or freedom from late reintervention.

Stather et. al. investigated the outcomes for a total of 552 patients, making up 2.3% of the total population from included studies. In their study the rate of interventions less than 30 days from the index procedure and over the long term was not significantly different between the SA and NSA groups however when they analysed the number of reinterventions (rather than number of patients undergoing reinterventions) they found that statistically significant more reinterventions were undertaken in the NSA vs SA group (37 (22.8%) vs 38 (11%), respectively,  $p = <0.01$ ). In that study they had a mean follow up of 4.1 years and although they found no difference in type 1 endoleaks less than 30 days from the index procedure they did find that significantly more patients in the NSA group developed a type 1 endoleak during follow up. Further analysis of reinterventions showed that significantly more reinterventions were undertaken for proximal type 1 endoleak in the NSA group vs SA group (5 (2.5%) vs 2 (0.6%), respectively,  $p = <0.05$ ). They also found

more reintervention procedures performed for type 2 endoleak in the NSA group. Over the length of their follow up more patients in the NSA group suffered a ruptured aneurysm vs SA group (7 (3.5%) vs 4 (1.1%), respectively). However, this failed to reach statistical significance with a p value of 0.05. Furthermore, there was no significant difference in migration, sac expansion, <30-day mortality, >30-day mortality or aneurysm related mortality over follow up. Additionally, there was no difference found for the number of reinterventions performed for, type 1b endoleak, limb occlusion, migration, type 3 endoleak or rupture.

In the remaining study to show a significant difference in reintervention rates Hobo et.al. investigated outcomes for 5183 patients from the EUROSTAR registry (comprising 21% of the total population of included studies). They investigated the role of “severe neck angulation” (>60 degrees beta angulation) on clinical outcomes. They found that severe neck angulation played no role in early reintervention rates (<30 days from the index procedure) but did in ‘late’ reintervention rates, beyond 30 days. The reintervention rate over the follow up was 13.6% in the NSA group versus 10.8% in the SA group, with an adjusted hazard ratio of 1.29 (95% CI 1 – 1.67). In that population there was also significantly more type 1 endoleaks found in the NSA group over the follow up but no difference in migration, rupture or mortality rates.

Of the remaining included studies, five did not compare reintervention rates between NSA and SA groups, three did not report on secondary interventions and 10 reported outcomes but did not show a significant difference between the NSA and SA groups. Interestingly, most showed an increase in proportion of secondary interventions over follow up in the NSA group versus the SA group, but it did not reach statistical significance. [68, 94, 113-117]. Abbruzzese et.al. showed in their study that as the number of parameters of IFU

violation increased the freedom from reintervention over the follow up period decreased. They compared 18 patients with 3 or more IFU violations with 343 patients with SA and found that the 5-year freedom from reintervention rates were 21% vs 85% respectively (p = 0.001).

#### **5.4.5. Graft related endoleak**

Two of the included studies did not report on any graft related endoleak at all [94, 98]. Of all the included studies that report on graft related endoleak no study found a significant difference between NSA and SA groups in terms of type 1b and type 3 endoleaks. There were three studies that specifically reported on type 1b endoleaks separately from type 1a endoleaks [68, 113, 122]. The range of type 1b endoleak beyond 30 days was 0.6% - 4% for SA patients and 4.2% - 7.2% for NSA patients. In three studies [103, 114, 119] “type 1” endoleaks are reported on but there is no definition as to whether this includes all type 1 endoleaks or only proximal endoleaks. Seven studies report specifically and separately on the occurrence of type 3 endoleaks [68, 103, 113, 114, 116, 121, 122]. The range of type 3 endoleaks reported beyond 30 days for SA and NSA patients respectively is 0 – 5.8% and 0 – 1.5%. Again, no statistically significant differences were found when comparing type 3 endoleaks over follow up. The following table details the reporting of type 1a endoleaks found before and after 30 days. Where possible the rates at standard time intervals is given, however often reports simply group endoleaks into <30 days and those found over the remainder of the follow up. (See table 5.12.)

**Table 5.12. Reporting of type 1a endoleaks from included studies**

Study	Length of FU, mean or median (Months)	N	SA pts - Type 1a Endoleak, n(%) (at varying time intervals)	N	NSA pts - Type 1a Endoleak, n(%) (at varying time intervals)	Significant difference between groups
<b>Pitoulis (NC), 2017[111]</b>	41	88	-	73	<30d: 4.1% 1-5yr: 2.7% Freedom at 3yr - 94.2%	N/A
<b>Gallitto (NC), 2016[112]</b>	51.4	-	-	60	<30d 3.3% 1 – 5 yr.: 1.7%	N/A
<b>Mateo (C), 2016 [113]</b>	SA - 30.5 NSA – 38	178	0	71	<30d – 0 5-10yr: 1.4%	NS
<b>Cerini (C), 2016 [95]</b>	37	94	<30d: 1.1% 1 – 5 yr.: 1.1%	115	8.8% All <30 d, all had neck length <10mm	0.04
<b>AbuRahma (C), 2016 [96]</b>	30	251	<30d: 7% >30d: 2% Freedom from type 1 >30d 1yr 99.5% 2yr 99.5% 3yr 98.4%	275	<30d: 18% >30d: 6% Freedom from type 1 >30d: 1yr 98.9% 2yr 98.1% 3yr 98.1%	<30d: <0.0002 >30d: 0.048 KM analysis: 0.049
<b>Broos (C), 2015 [114]</b>	12	1114	<30d: 0.7%	104	<30d: 7.4%	Significant
<b>Walker (C), 2015 [115]</b>	36	284	Type 1 or 3 during FU: 3.5%	205	Type 1 or 3 during FU: 4.4%	NS

<b>Speziale (C), 2014 [116]</b>	24	63	<30d: 0 1-5yr: 1.6%	133	<30d: 0 1-5yr: 3%	NS
<b>Lee (C), 2013 [117]</b>	35	143	>30d: 5.6%	75	>30d: 5.3%	NS
<b>Antoniou (C), 2013 [118]</b>	18	-		60	1 (1.7%)	N/A
<b>Stather (C), 2012 [103]</b>	SA – 48.8 NSA – 50.1	353	<30d: 0.8%) >30d: 4.5%	199	<30d: 2.5% >30d: 9.5%	<30d NS >30d = 0.02
<b>Hager (C), 2012 [119]</b>	18.6	-		84	<30d: 7.1%	N/A
<b>Forbes (C), 2010 [120]</b>	51.6	250	<30d: 1.6%	68	<30d: 5.8%	NS
<b>Chisci (C), 2009 [121]</b>	19.5	0		74	<30d: 4.1% >30d: 5.4%	N/A
<b>Hobo (C), 2007 [67]</b>	19.9	4031	<30d: 1.9% >30d: 3.2%	1152	<30d: 4.9% >30d: 6.5%	<30d =0.0001 >30d =0.0016
<b>Choke (C), 2006 [122]</b>	21.7	87	<30d: 2% >30d: 1%)	60	<30d: 3% >30d: 3%	NS

<b>Leurs (C), 2006 [68]<sup>a</sup></b>	12	2872	<30d: A=2.6%  >30d: A=3.4%	677	<30d: B= 3.5% C =10.9%  >30d: B = 9.6% C = 11.3%	<30d: C vs A, [OR 4.46 (95% CI 2.61 - 7.61)]  >30d: B vs A, [OR1.98 (1.16-3.38)]  C vs A, [OR 2.32 (1.17- 4.6)]
<b>Fairman (C), 2004 [106]</b>	21	66	15.2%	153	10.5%	NS
<b>Dillavou (C), 2003 [110]</b>	18	115	<30d: 1.7%  >30d: 0.8%	91	<30d: 1.1%  >30d: 2.1%	NS

Table 5.12 - SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS – Not Significant, NR – Not reported, FU – Follow up, a – Leurs et.al. compared three groups with different neck lengths, (A) – >15mm, (B) – 10 – 15mm, (C) - <10mm.

The total cohort of SA patients is 16053 and NSA patients is 8458 across all included studies. However, when only considering those studies in which there is comparison between SA and NSA patients there are 10244 SA patients and 3600 NSA patients. Five studies showed that NSA patients have significantly more type1a endoleaks within 30 days from the procedure compared with SA patients. These studies comprise 8362 SA patients (81.6% of the SA patients where comparison with SA was being drawn) and 2323 NSA patients (64.5% of the total). Four studies show the same to be true over the course of follow up beyond 30 days and they comprise 7507 SA patients (73% of the total) and 1303 NSA patients (36% of the total). The range of observed type 1a endoleaks is as follows:

- SA patients (<30 days) – 0 – 2.6%
- NSA patients (<30 days) – 0 – 10.9%

It should be noted that one study [96] included all intraoperative type 1a endoleaks whether treated successfully or not. The rate of type 1a endoleaks in that study for SA patients was 7% and NSA patients 18%.

The range of observed type 1a endoleaks >30 days is as follows:

- SA patients – 0.8 – 5.6%
- NSA patients – 1.4 – 11.3%

In one study, by Fairman et. Al. the reported endoleak rate for the SA group was 15.2% but this was for all endoleaks at all points and no distinction was made between perioperative endoleaks within 30 days and those found throughout follow up.

## 5.5. Secondary Outcome Results

According to published reporting standards [24], primary technical success is defined as “successful introduction and deployment of the (endovascular) device in the absence of; surgical conversion, mortality, type 1 or 3 endoleaks and graft limb obstruction.” The reporting standards also state that if unplanned endovascular or surgical procedures are necessary then the terms “assisted primary or secondary technical success, respectively, should be used.” For the purposes of this systematic review it is this definition that is used when determining rates of technical success. In general, across the literature authors poorly defined technical success in their report and in some instances were clearly contrary to the published reporting standards. It should be noted these accepted reporting standards were published in 2002, before all the included articles. Primary technical success was reported on or possible to gather from presented data in 11 of the included studies. Primary technical success for SA patients ranged from 89.7 – 99.7% [95, 107, 116,

120, 122]. In two cases where primary technical success was reported as 89.7% and 90.5% the assisted primary technical success rate was also reported and was 100% in both cases. For the NSA group 10 studies reported on primary technical success rates and they ranged from 80 – 98% [95, 103, 111-114, 116, 119, 121, 122]. The total combined primary technical success rate was 962 patients out of 1061 (90.7%). Five of these studies also documented additional unplanned endovascular procedures bringing their assisted primary technical success rate to 100%. [111-113, 116, 119]. One additional study reported an assisted primary technical success rate of 98%. [122] From these six studies it is possible to analyse the reasons for lack of technical success; in no study was there a statistically significant difference between the SA and NSA groups in terms of technical success but one study [113] did show a significant difference in the number of proximal cuffs placed for type 1a endoleak seen on completion angiogram; In the SA group 4 (2.2%) patients had an intraoperative extension cuff placed, compared to 7 (9.9%) NSA patients (OR 4.76, 95% CI 1.3 to 16.8, p=0.014). From these six studies, comprising 328 SA patients and 481 NSA patients, there was a total of 19 unplanned adjunctive procedures performed for the SA group (5.8%) and 78 for the NSA group (16.2%). Of all the 97 adjunctive procedures, 75 were for lack of proximal seal and 22 were for iliac issues. Of the 75 procedures for lack of proximal seal on completion angio; 34 were placement of an extension cuff, 16 were placement of a large palmaz stent, 2 were additional proximal balloon moulding, 1 was the placement of embolization coils and 22 procedures were not specified in the report.

Although clinical success as per the reporting standards was defined as a secondary outcome measure at the beginning of the systematic review not a single included study reported clinical success rates as per the reporting standards. Due to the multiple requirements for clinical success to be achieved it was not possible to ascertain the true clinical success over the follow up for any given population in the included studies. Therefore, no further analysis can be made of it here. Similarly, the length of hospital stay

was very infrequently reported, and little can be made of further analysis in this systematic review. Rates of visceral vessel patency were rarely reported specifically. However, for completeness, the results of the 5 studies that commented on visceral vessel events are presented here [95, 106, 112, 117, 121]. There were 2 patients with renal artery occlusion in SA patients perioperatively (of 303 patients, 0.7%) compared with 10 NSA patients (of 477, 2%). In only one study was there mention of visceral vessel events during follow up, the remainder pertained to perioperative events.

Only one study showed a significant difference in terms of renal dysfunction between the SA and NSA groups [106]. That study focussed specifically on renal outcomes and a 'renal event' was defined as *"renal artery occlusion, new parenchymal infarction visible on computed tomography (CT) scan, including segmental and small wedge-shaped infarcts; acute increase in serum creatinine concentration to greater than 2 mg/dL; and transient or new-onset uncontrolled hypertension."* They found that NSA was associated with an increased risk of any renal event at any time point (13.6% SA patients vs 27.5% of NSA patients,  $p= 0.04$ ). The majority of events were a rise in creatinine with 100% of the SA patients and 74% of the NSA patients suffering this. Unfortunately, the study does not clarify what clinical sequelae, if any, these patients suffered from this increased rate of renal events. Of the remaining studies; one reported permanent deterioration in renal function rates as high as 8.1% [121] occurring perioperatively but noted no dialysis resulted from this. One other study [95] showed that 3 NSA patients (2.6%) went on to require dialysis after occlusion of a renal artery.

### **5.5.1. Endograft Migration**

Most studies reported no or little stent graft migration both in the short term and throughout follow up (See table 5.13.)

*Table 5.13. Rates of endograft migration reported in included studies*

Study	Length of FU, mean or median (Months)	N	(SA patients) Migration reported through FU, %	N	(NSA patients) Migration reported through FU, %	Significant difference between groups
Pitoulas (NC), 2017[111]	41	88	-	73	0	N/A
Gallitto (NC), 2016[112]	51.4	-	-	60	0	N/A
Mateo (C), 2016 [113]	SA - 30.5 NSA – 38	178	0	71	0	NS
Cerini (C), 2016 [95]	37	94	0	115	0	NS
Broos (C), 2015 [114]	12	1114	0	104	0	NS
Speziale (C), 2014 [116]	24	63	0	133	6.4%	NS
Lee (C), 2013 [117]	35	143	2.1 %	75	2.7%	NS
Antoniou (C), 2013 [118]	18	-	-	60	0	N/A
Stather (C), 2012 [103]	SA – 48.8 NSA – 50.1	353	2.5%	199	3.0%	NS
Hager (C), 2012 [119]	18.6	-	-	84	0	N/A
Chisci (C), 2009 [121]	19.5	-	-	74	2.7%	N/A
Abbruzzese (C), 2008 [94]	29.6	343	2.1%	222	1.4%	NS

<b>Hobo (C), 2007 [67]</b>	19.9	4031	<30d: 0.8% >30d:4.3%	1152	<30d: 1.6% >30d: 5.9%	<30d = 0.0105 >30d - NS
<b>Leurs (C), 2006 [68]</b>	12	2872	2.8%	677	1.2%	NS
<b>Fairman (C), 2004 [106]</b>	21	66	<30d: 0 Free (2yrs): 86.9%	153	<30d: 0 Free (2yrs): 87%	NS
<b>Dillavou (C), 2003 [110]</b>	18	115	0	91	0	NS

Table 5.12 - SA – Standard Anatomy, NSA – Non-standard anatomy, AAA – Abdominal aortic aneurysm, NS –

Not Significant, NR – Not reported, FU – Follow up

One study by Hobo et.al. found a significant difference between SA and NSA groups in terms of migration within the first 30 days. This study was a review of the large EUROSTAR registry investigating the effect of beta angle >60 degrees on outcome. Although this study found an increase in migration in the short term in NSA patients this difference was not sustained beyond 30 days. The authors offered no explanation for why this may be the case, but this may be due to the fact this was a registry-based study on a large number of patients and therefore resolution of individual patient data is inevitably less good in such a study.

### 5.5.2. Conversion to Open Repair

Of all the included studies, five of them did not report on conversion to open repair rates. [67, 96, 98, 115, 122] In some cases this may have been because there was no conversion to open repair, however without explicit statement of this it could not be assumed. The remaining 16 studies reported on conversion to open repair rates. Of 7935 patients (both SA and NSA) across those studies 93 cases of conversion to open repair were documented giving an overall rate of 1.2% across all time points. This included perioperative

conversions, within 30 days and beyond. Some studies did not clarify whether the conversions were in SA or NSA patients. In any studied that statistically analysed the difference between SA and SNA patients and the rate of open conversion there was no statistical difference. [68, 94, 106, 114] In 15 cases the reason for conversion was known but not mentioned in the remaining 78 cases. Reasons given for conversion included;

- Access related failure during index procedure (2 patients)
- Delivery system failure (device related failure) intraoperative (1 patient)
- Bilateral renal artery coverage during index procedure (1 patient)
- Infected endograft necessitating explantation (2 patient)
- Proximal endoleak without rupture (4 patients)
- Presentation with ruptured aneurysm (1 patient)
- Presentation with proximal endoleak and ruptured aneurysm (4 patients)

### 5.5.3. Aneurysm Growth

Seven of the included studies did not report on aneurysm growth or reduction over time. Of the studies that did include it in their report there was significant variation in the reporting of changes in aneurysm dimensions. One reported rates of aneurysm enlargement using a definition of >8mm to define what constituted an enlarging aneurysm [68], another studied defined an enlarging aneurysm as growth >2mm [111]. In addition to this AbuRahma et.al. utilised Kaplan Meier analysis of freedom from “sac enlargement” while most other studies reported a proportion of patients with “sac enlargement”.

Chisci et.al. who reported on outcomes of open repair, standard EVAR and fEVAR for NSA showed that in their study standard EVAR had a higher incidence of ‘late sac expansion’ compared with fEVAR (9 (12.2%) versus 1 (1.9%),  $p=0.036$ , respectively). Of note the largest study identified and included in the systematic review [98] identified a significant proportion of NSA patients with aneurysm enlargement over the course of follow up. In the

entire cohort of their studied population, including SA and NSA patients they found that the proportion of patients exhibiting aneurysm enlargement at 1, 3, and 5 years after EVAR were 3%, 17%, and 41% respectively. They also noted that 30% of patients did not demonstrate enlargement until 3 years after their index procedure. They also showed that aneurysm enlargement was more common in patients with NSA anatomy compared to SA anatomy. Interestingly they also found a correlation between year of endograft implantation and AAA enlargement over follow up, showing that those stent-grafts implanted after 2004 had a higher rate of expansion than those placed before this date. This study performed univariate and multiple variable analysis and determined the following predictors of AAA enlargement post EVAR; presence of endoleak on any post-operative scan (HR 2.7, 95% CI 2.40 – 3.04), patient age >80 years, aortic neck diameter >28mm, beta angulation >60 degrees and anatomy outside IFU.

## **5.2. Summary of results**

In summary; 21 studies were included in the final systematic review with a total population of 24511 patients. The number of patients with SA was 16053 and there were 8458 with NSA. The length of follow up within studies ranged from 12 months – 51.6 months. No significant difference was found between SA and NSA patients with regards to perioperative mortality with total rate of perioperative death being 2.3% in SA patients and 3.1% in NSA patients. The rates of aneurysm related mortality throughout follow up were similar between the two groups also, with only one study revealing a significantly increased ARM in the NSA population, though the reporting of ARM was inconsistent within that study and when compared to other studies and published reporting standards. The rates of all-cause mortality throughout follow up were similar between the two groups also; the five-year survival rate was between 70 – 85% for NSA patients and approximately 85% for SA patients.

It appears from the collated results there may be an increased risk of secondary intervention during follow up (beyond 30 days) in NSA patients treated with standard EVAR. A large registry study (Hobo) found increased reintervention rates with a HR of 1.29 (95% CI 1 – 1.67) for NSA patients. The remaining studies did not show a statistically significant difference, but all reported increased reintervention rates in the NSA group compared with SA patients. Often the increased reintervention was attributed to an increased number of procedures performed for the purposes of maintaining or achieving proximal seal.

From the included studies it appears that type 1a endoleak rates are higher in patients with NSA treated with standard EVAR compared to SA patients. A maximum type 1a endoleak rate for NSA patients versus SA patients was 10.9% vs 2.6% respectively within 30 days. The difference beyond 30 days was 11.3% versus 5.6% for NSA and SA patients respectively.

A large image repository-based study comprising the majority of included patients (schanzer) found that NSA anatomy seemed to predict aneurysm enlargement over the course of follow up (31 months in that study), as well as presence of endoleak and age >80 years.

### **5.3. Discussion**

Two previous systematic reviews and meta analyses have been done in this area, to investigate the differences between SA and NSA patients undergoing standard EVAR [57, 78]. They were both published in 2013 with the most recent included article being from 2012. Antoniou et.al. included 7 articles with a total of 1559 patients and the primary findings from that meta-analysis were that NSA patients require an increase in intraoperative adjunctive procedures, they have an increased 30-day morbidity from their procedure and the rate of type 1 endoleak and aneurysm related mortality are increased at 1 year. The authors go on to conclude that insufficient high-level evidence exists and that

*“EVAR should be used cautiously in patients with unfavourable aneurysm neck anatomy”.*

The other meta-analysis by Stather et al. included 16 articles with a total of 11959 patients. Their principle findings were that patients with NSA had an increased 30-day mortality rate, increased use of intraoperative adjunctive procedures and an increase in 30-day migration rates. They also found that the rate of both 30 day and “late” type 1 endoleaks were increased in NSA patients. The authors go on to conclude: *“performing EVAR in patients with unfavourable neck anatomy results in poorer short-term outcomes. The higher rates of early and late type I endoleaks suggest that increased monitoring should be performed in this category of patient.”*

The current systematic review includes 10 papers published since 2012 and a total of 24511 patients that makes it the largest systematic review in this area. No randomised controlled trials have been identified that investigated the differences between NSA and SA patients undergoing standard EVAR and all the included studies in this systematic review are observational non-randomised studies. The results from any synthesis of the literature therefore needs to be read with this in mind.

This systematic review sought to define the study populations of NSA and SA based on manufacturers recommended instructions for use criteria. In fact, one important point to note is that there was significant heterogeneity across the included studies as to what was determined “hostile” or “bad” neck anatomy. This, in itself, therefore limits the validity and applicability of any synthesis of results across the studies. In fact the two meta analyses mentioned above [57, 78] differ on this exact point with one using the IFU definition for inclusion into their meta-analysis [78] and the other preferring set anatomical criteria [57]. Stather et. al. even goes on to criticise the meta-analysis by Antoniou et.al. in this regard stating that:

*“A major limitation of Antoniou’s study is that the included studies defined hostile neck if a device-specific analysis had been conducted; otherwise, studies had to include neck length <15 mm and neck angulation >60°. Patients were thought to have HNA (Hostile neck anatomy) if one or more criteria were present. In addition, the lack of inclusion of patients with increased neck diameter limits the generalizability of these results. Our study, therefore, aimed to address these limitations by including any of the HNA criteria.”*

Stather et. Al. used specific set anatomical criteria to define whether anatomy was NSA or SA and included in their definition any proximal neck diameter of >28mm even though most stent-grafts at the time of their publication included neck diameters up to 32mm in their IFU. It is true that most of the included studies in their systematic review were published before 2008 and prior to this time most implanted stent-grafts had IFUs that would consider >28mm as a breach of that particular guideline. However, it does mean that some patients included in their study as having a “hostile” neck would have been treated by a clinician implanting a stent-graft within its IFU. If one was investigating the specific outcomes relating to specific anatomical parameters (e.g. neck diameter, or angulation or length) then a specific measurement value would be a valid defining criterion and analysis of the performance of different stent—grafts inside and outside that specified parameter would be an inherent and interesting part of the analysis. However, when the criteria of interest is “hostile” neck anatomy there is essentially a choice as to how one defines that – with specified anatomical values regardless of what stent-graft is implanted or anatomical criteria that vary depending on stent-graft implanted i.e. the IFU. If the former definition is applied this methodology would essentially ignore the fact that stent-grafts differ in their design and have been tested by the manufacturers against certain tolerances both ex vivo and in vivo. However, it potentially allows the analysis to define if there are finite limits to anatomy in which EVAR can be used. If utilising IFU for the definition of NSA then,

potentially less can be said about specific anatomical thresholds that may or may not impact on clinical outcomes.

In endovascular surgery technological advancement is relatively rapid and evolution of the devices in question happens at a pace that outstrips the publication of clinical outcome data for a given device. This means that meaningful collation of large quantities of clinical outcome data, as in a systematic review, needs a way of handling the potential confounding factors of differing anatomy and stent-grafts used. Utilising IFU allows different stent-grafts to be compared using a common characteristic regardless of the anatomy being treated, i.e. inside or outside IFU. It is for these reasons that this author recommends that studies investigating this area should use IFU as the anatomical definition for “good” vs “bad” anatomy. At all points the IFU for each device being considered should be published to allow retrospective review to understand the characteristics considered “out of IFU” or that stent graft when it was implanted – as newer versions of the same stent graft may be released onto the market at a later date and it can be difficult to retrospectively source the IFU for a given time period from the manufacturer. Another comment to make about this is that there is no reason that specific IFU criteria (and therefore individual anatomical criteria such as angulation cannot be analysed within such a study) for example comparing less than 60 degrees of beta angulation with greater than 60 degrees but ensuring that all patients within the <60 degrees group are within IFU for all variables and that those within the >60 degree group are out of IFU for the stent graft used. It is the opinion of this author that populations should still be assessed and grouped whether they fulfil all IFU criteria or not. This does limit numbers of patients available for analysis but this ‘tool’ acts to control for the confounding factors of other anatomical features, which can affect outcomes.

The significant heterogeneity seen in the included studies was also evident in a number of areas. The methodological quality across the studies was relatively poor. Often studies would include patients treated as an emergency and not separate the data for those patients to allow separate analysis. Also, it was often not defined at all whether emergent patients were included or not. Definitions were reported in the main to follow published reporting standards however further analysis of the data revealed importantly that these definitions were sometimes inconsistently applied for example in the labelling of patients as having suffered aneurysm related mortality or not. Studies often did not state whether reviewers who analysed CT scan data were blinded to the clinical outcomes and studies consistently scored poorly in this domain when assessing their quality using the MINORS tool. Due to significant heterogeneity in the definitions and reporting of inclusion criteria, and outcome measures it was decided early in the process of performing this systematic review that a narrative account rather than a meta-analysis should be undertaken. In the meta-analysis by Antoniou et.al. mentioned earlier the authors found that only a limited number of studies (and patients) could be included for any given outcome measure they were investigating because of the disparities and inaccuracies in reporting in the wider literature. This limited the conclusions that could be drawn from that meta-analysis. Furthermore, Stather et.al. in their systematic review cited the fact that studies defined NSA differently introducing an important confounding factor into the systematic review and subsequent meta-analysis. They found that when they analysed only studies that included “all three” neck criteria of diameter, length and angulation, this reduced the number of studies analysed to 5 and with a patient cohort of 1995. They do state however that many of their principle findings were maintained when this analysis was done. Furthermore, the length of follow up was relatively short in the majority of studies with 10 studies reporting a mean or median follow up of 2 years or less and 16 reporting 3 years or less. With reporting standards [99] defining follow up of between 1 and 5 years as “short

term” when EVAR is implanted electively it highlights the limited nature of this and other systematic reviews in determining outcomes over the longer term.

From the included studies there were 4 more recent studies that detailed and showed a significant difference in the use of proximal aortic cuffs between the NSA and SA groups. [96, 113, 114, 117]. There were 2 other studies that failed to show a statistically significant difference and the rest did not report on the use of aortic cuff extensions. Of the four studies mentioned above they showed that 36 out of 1686 SA patients (2.1%) had a cuff placed either intraoperatively or within 30 days of the original procedure. This compares to 67 of 525 NSA patients (12.8%). It is reported by Broos et.al. that there were no significant differences in technical success rates and it appears that the majority of these extension cuffs were placed intraoperatively. This suggests that they were successful in most of the cases to help achieve a proximal seal on the day of the index procedure. As noted earlier however there was a significantly higher type 1 endoleak rate within and beyond 30 days in the NSA group. What is difficult to ascertain is whether the higher endoleak rate within 30 days is despite the extra use of proximal aortic cuffs or whether these extra cuffs are being placed to treat these extra type 1 endoleaks. However, because of the higher rate of endoleaks after 30 days it seems clear that whatever the scenario in the perioperative phase, despite aggressive treatment of the proximal seal zone, these devices do continue to fail at a higher rate than their SA counterparts resulting in more type 1 endoleaks.

It seems intuitive that if an aneurysm presents anatomy that fails a number of anatomical IFU criteria rather than just one it will have a greater risk of poor clinical outcomes. This supposition cannot be determined from the available literature. One study [116] did show significantly worse outcomes as the number of IFU violations were increased but the subsequent analysis included only small numbers of patients as the majority were out with

IFU on only 1 anatomical criterion. This is an important area for future research to determine truly what the additive effect of increasing IFU breaches is.

There were several limitations within this systematic review. As stated previously there was significant heterogeneity within the literature in terms of the reporting of anatomical characteristics and between publications in terms of the focus of their analysis conducted (anatomical values vs in or out of IFU). To enable the inclusion of as many potentially relevant studies while trying to minimise the potential for confounding factors in terms of anatomical factors, inclusion criteria were drawn up to allow the inclusion of studies if they specifically reported anatomical values that were out with the IFU for the implanted device. In reality this led to the inclusion of some studies, most notably the EUROSTAR series' [67, 68], that investigated individual anatomical factors (neck length and angulation) and included NSA patients in their "SA" group. To limit the inclusion to studies in which only SA patients were in the "SA" group would have significantly limited the number of patients included in the final analysis and thereby would have potentially ignored important results from these studies that are valuable and useful when analysed with this confounding factor in mind. Such as the findings of increased graft related endoleaks in those patients with short or angulated necks. This systematic review could also be criticised for the inclusion of the paper by Schanzer et.al. as this one paper contributed such a large proportion of the patients and was distinctly different in its methodology and patient capture than the others. This study utilised an imaging repository in the United States of America, to investigate anatomical features found pre and post EVAR in a large number of patients. Little is known about the clinical circumstances of the patients or even the type of endovascular device implanted. Therefore, there was only really one outcome measure analysed in this study – aneurysm growth over time. It was included because it indeed did meet the pre-specified inclusion criteria, but the value of its inclusion was very limited despite the number of patients it contributed. Without the inclusion of that study this

systematic review would have included 20 studies with 14283 patients (10332 SA patients and 3951 NSA patients). In addition to these criticisms the study by Schanzer et. al. included a large proportion of patients (59%) with AAA less than 55mm in diameter. Since the current indication for treatment is AAA >55mm electively the addition of these patients limits the applicability of the findings from that study to most patients treated today.

This systematic review sought to analyse demographic and anatomical data in relation to NSA patients undergoing standard EVAR and also sought to compare outcomes for these patients with SA patients undergoing EVAR but arguably this is an irrelevant comparison. Most vascular surgeons would not argue that clinical outcomes after surgery are inferior when dealing with more complex anatomy, and this is especially true in aneurysm surgery. Reports within the first five years of EVAR use becoming widespread began to show this [97] and it has been continually confirmed by further reports detailed here in this systematic review and in other systematic reviews [57, 78]. Therefore, comparison of outcomes between SA and NSA patients undergoing standard EVAR provides value in knowing the magnitude of the deleterious effects of performing EVAR in this population and where if any thresholds of anatomy cannot be breached in any circumstances. If one accepts that NSA patients have inferior outcomes when treated by standard EVAR compared to SA patients the next question is whether those outcomes are inferior to the outcomes for alternative treatments for NSA patients. Therefore, comparison with the alternatives such as open repair, standard EVAR with auxiliary techniques and devices (e.g. endoanchors), advanced stent graft techniques (chimney EVAR, fEVAR and distinct technology such as endovascular aneurysm sealing is the important next step in research for these patients.

## 5.4. Conclusion

In conclusion, there is limited high quality evidence to suggest what the magnitude of difference in outcomes there are between NSA and SA patients who undergo standard EVAR. It appears that there is a difference in outcomes when comparing the two groups. Primarily NSA patients experience an increased rate of type 1a endoleak both within 30 days from the index procedure and beyond. They also experience an increased risk of secondary intervention, usually to maintain proximal seal. There is insufficient evidence to suggest whether these findings equate to significantly worse outcomes for NSA patients in terms of all cause or aneurysm related mortality beyond 30 days. The data on outcomes from these patients are currently only available for short term (up to 5 years post operatively) and therefore to better understand long term outcomes and risks in these patients further study and research is needed. This should analyse patients defined by anatomy relating to the IFU for the device implanted to allow comparisons of patients across a time period which has seen significant advances and evolution in technology.

## **6. CHAPTER 6 - Systematic Review of Clinical Outcomes Following Open Surgical Repair in Non-Standard Aneurysms**

### **6.1. Introduction**

As stated in the above systematic review it is important to compare outcomes for patients with NSA across different treatment options to understand what the shortcomings are of each treatment. The purpose of this research as a whole is to try and answer that question and specifically to investigate the clinical outcomes for three treatment options for patients with NSA: namely EVAR outside instructions for use, open surgical repair and fenestrated endovascular aneurysm repair. Open surgical repair has been performed on abdominal aortic aneurysms for many decades but gained prominence in the 1950's with Dubost [56]. Since then it has been the mainstay of treatment for abdominal aortic aneurysms until the advent of endovascular techniques. By many open repair is still considered the gold standard and therefore it is important to understand the clinical outcomes for patients with NSA treated with open surgical repair to allow comparison with the other two treatment options described. The aim of this systematic review was to provide an updated synthesis of the available evidence from contemporaneous (20-year search limit) reports and previously conducted systematic reviews and meta-analyses investigating specifically the clinical outcomes for aneurysms that possess NSA.

The question being addressed in this systematic review is to understand what the clinical outcomes are for patients undergoing open surgical repair whom exhibit proximal aortic neck anatomy that is considered outside the indications for use for standard EVAR. The primary clinical outcome measures will include the following both perioperatively and throughout follow up; all-cause mortality, aneurysm related mortality, and reintervention rates. Secondary outcome measures will include: visceral vessel patency (where reported), rates of renal dysfunction. The systematic review also aims to investigate by its narrative

nature the quality of reporting of anatomical detail with regard to the proximal aortic neck in the available literature to determine if current standard reporting within the published literature allows comparison between truly anatomically homogenous groups. This systematic review was conducted in a similar way to the above reported review looking into outcomes after standard EVAR used in NSA.

## **6.2. Methods**

The systematic review followed reporting guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) document. [108] In line with these guidelines a protocol for the systematic review was established prior to the beginning of the literature search as follows. The protocol is reproduced here in its entirety.

### **6.2.1. Protocol for Systematic Review, Including Eligibility Criteria**

A systematic review of the literature will be undertaken to examine the clinical outcomes for patients undergoing abdominal aortic aneurysm repair for non-standard aneurysms using open surgical repair. Non-standard aneurysms are defined as those in which the aortic neck anatomy is considered outside indications for use (IFU) criteria for standard infrarenal EVAR. Primarily this includes those aneurysms with a neck length of less than 10mm from the lowermost renal artery ostium to the top of the aneurysm, neck diameter of >32mm and or angulation of >90 degrees between the infrarenal neck and the aneurysm itself. An aneurysm would be considered non-standard if any of these criteria are present. It is expected that within the published literature there may not be detailed anatomical criteria included in the reports and therefore it will be difficult to truly identify whether a study will include patients in whom the anatomy would have been suitable for standard endovascular repair. Therefore, the anatomical definitions used in a study will be scrutinised and if there is not enough clarity to ensure that the patients being studied truly

do have NSA then that study will be included. If a study includes patients in whom both NSA and SA are being investigated, then only if the results for patients with NSA can be ascertained from the published report then that study will be included. In the absence of reporting of specific anatomic criteria such as neck length, diameter or angulation a few other anatomic classifications will be accepted to reasonably suggest that NSA is being investigated. These will include the term “juxtarenal” and “pararenal” aneurysm as defined by the Ad Hoc Committee on Reporting Standards for the Society of Vascular Surgery [24]. This definition states that there is “no normal aorta between the upper extent of the aneurysm and the renal arteries”. Aneurysms defined as suprarenal will not be included as this description suggests the aneurysm involves the visceral segment of aorta and therefore, if treated endovascularly, would require branched endovascular technology, not fenestrated technology. Furthermore, aneurysm described as type IV thoracoabdominal aneurysms will not be included for the same reason. The caveat to this is if an aneurysm is defined as suprarenal but specific anatomic criteria are reported to clarify that actually fenestrated endovascular repair could be performed within its IFU.

The objective of the systematic review is to compare the published literature for all patients with non-standard aneurysms undergoing open surgical repair. It is expected that no randomised controlled trials would be identified and therefore non-randomised studies evaluating clinical outcomes would be included in the analysis.

Inclusion criteria:

- Aneurysm morphology - For a study to be included in the analysis, it should clearly state that the population had morphologic infrarenal neck characteristics that were not within the indications for use for standard EVAR. As already stated above other definitions will be accepted in line with published reporting standards.

- There must be median (or mean) follow up of at least 1 year to enable meaningful results of short and mid-term data for the studied population
- In order to reduce bias introduced from small case series studies must have at least 50 patients with non-standard anatomy

#### Exclusion Criteria:

- Studies reporting solely on symptomatic or ruptured aneurysms. If a study includes symptomatic or ruptured aneurysms it is expected that the results for these patients will be identifiable and be able to be excluded from further analysis. If it is not possible to do so then an explicit statement as such will be made in the report to make it clear that this confounding variable exists in the identified study population.
- Previous treatment for abdominal aortic aneurysm
- If the report presents patients treated with a hybrid (endovascular combined with open surgical repair) technique.
- Aneurysms repaired by laparoscopic means will be excluded from the analysis
- No statement of aneurysm morphology, either as “outside IFU” or specific anatomic criteria

#### Eligibility Criteria

- Publication dates within 20-year period (1998 – 2018)
- English language only results considered
- The population will include all adults with no age restriction

The above protocol was referred to throughout the data identification and extraction phase to ensure it was adhered to.

### **6.2.2. Definitions and Outcome Criteria.**

Outcome criteria and definitions were based on recommended reporting standards for EVAR, published by the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery [24] which include details on reporting outcomes for open surgical repair also. The outcomes within the first 30 days after the index procedure or occurring within the same hospital admission will be reported as perioperative outcomes, those occurring between 30 days and 1 year will be termed 'Early', those between 1 and 5 years will be termed 'Short', 5 to 10 years will be considered 'Midterm' and > 10 years will be 'Long-term'. This is in line with the pragmatic minimum reporting standards for endovascular aneurysm repair [99] Primary outcome measures included perioperative mortality from any cause, all-cause mortality, aneurysm related mortality and reintervention rates. The secondary outcome measures are as follows:

- Primary Technical success
- Clinical success
- Visceral vessel patency
- Length of hospital stay
- Rates of renal dysfunction throughout follow up (the definition used within the given study for renal dysfunction will be used)

### **6.2.3. Information Sources and Electronic Search Strategy**

An electronic search of the literature was undertaken. The search was applied to MEDLINE (database provider PubMed, from 1998 – 2018) and EMBASE (database provider Ovid, from 1998 to 2018). The search was undertaken once in May 2018. A full record of the search strategy is included within Appendix 2. The full reference list of each full text study assessed was interrogated to identify any relevant articles missed in the original search.

#### **6.2.4. Study Screening and Selection**

The study screening and selection strategy employed was exactly that as for the systematic review of clinical outcomes of non-standard aneurysms treated by EVAR (Chapter 5). The search strategy results and reasons for exclusion are listed in figure 6.1 below.

Figure 6.1. Search strategy for Systematic Review of Open Repair used outside IFU

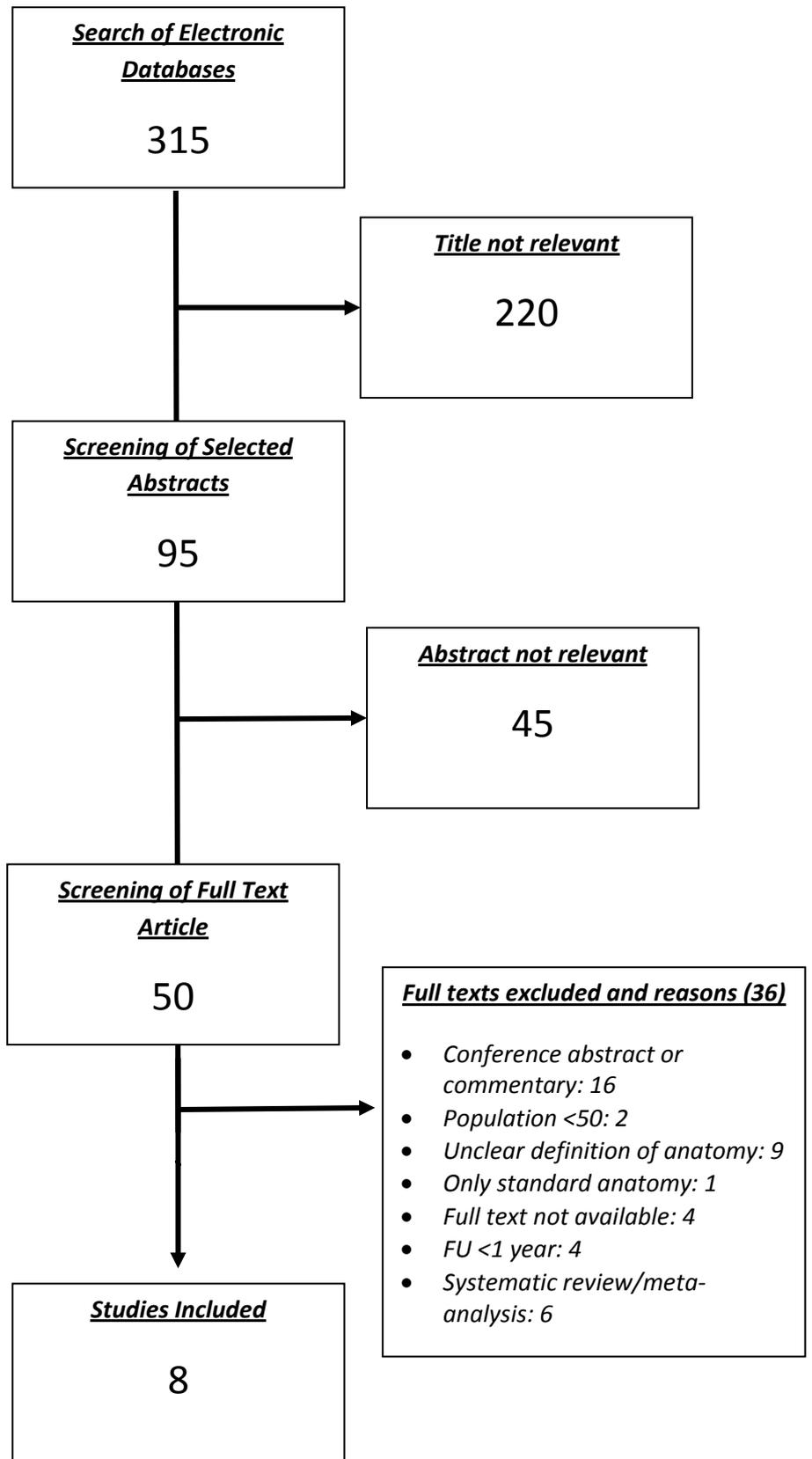


Figure 6.1 - Numbers represent articles. Arrows denote whether articles were excluded or included.

### 6.2.5. Data collection

A data extraction sheet was developed. As well as pertinent information relating to the publication (year of publication, journal etc) the remaining collected variables were divided in three broad categories: (1) baseline clinical and demographic data, anatomic characteristics, and procedure related characteristics; (2) primary outcome data (3) secondary outcome data, as outlined previously. The methodologic quality of the included studies was assessed using the MINORS tool. [109]

## 6.3. Results

From the 315 results returned from the original search 8 studies were included within the final analysis after full text review. [123-130] Regarding the 8 original studies included; there were 5 non-comparative and 3 comparative studies. Two of the three comparative studies compared juxtarenal aneurysms with infrarenal aneurysms treated by open repair [129, 130] and one study compared open repair with standard EVAR for juxtarenal aneurysms [128]. The year of publication ranged from 2007 – 2018 and most studies were conducted in the U.S.A. Patients were treated between 1986 - 2013. No randomised controlled trials were identified, and all studies were retrospective single centre cohort studies with the exception of one which was a multicentre retrospective cohort study. There were two studies that did not report the total number of aneurysm patients treated during the study period. Of the remaining 6 studies there was a total of 6608 patients treated during the study periods. From these 6 studies 867 (13.1%) patients were defined in a variety of ways to possess juxta or pararenal aneurysms to satisfy the inclusion criteria of this systematic review. From all 8 included studies the total number of subjects deemed to have NSA was 1150. Details of the included studies are shown in the table below (see table 6.1)

**Table 6.1. Details of included studies**

<b>Study</b>	<b>Years Recruited</b>	<b>No. patients</b>	<b>Comparative /Non-comparative</b>	<b>MINORS score</b>	<b>Definition of anatomy to include patient in “NSA” group</b>
<b>Sugimoto, 2018 [123]</b>	2007 – 2015	108	Non	8	Clamp above at least one renal
<b>Kabbani, 2014 [124]</b>	1986 - 2013	127	Non	4	No infrarenal neck suitable for clamping
<b>Speziale, 2010 [125]</b>	2000 - 2009	92	Non	7	Aneurysm up to renal arteries and clamp above at least one renal
<b>Knott, 2008 [126]</b>	2001 - 2006	126	Non	8	Aneurysm up to renal arteries and clamp above at least one renal
<b>Pearce, 2007 [127]</b>	1996 - 2006	134	Non	10	Clamp above at least one renal
<b>Sultan, 2011 [128]<sup>a</sup></b>	2001 - 2009	66	Comparative	15	Clamp above at least one renal
<b>Deery, 2016 [129]<sup>b</sup></b>	2003 – 2011	340	Comparative	13	Clamp above at least one renal
<b>Jeyabalan 2011 [130]<sup>c</sup></b>	2000 - 2007	157	Comparative	15	Aneurysm up to renal arteries and clamp above at least one renal

**Table 6.1 – NSA – non-standard anatomy. A – Comparing open repair with EVAR, b – Comparing infrarenal and pararenal open aneurysm repair, c – Comparing infrarenal and “complex” open aneurysm repair**

All of the included studies scored relatively poorly on the MINORS tool for assessing study quality suggesting they were all of poor methodological quality. Furthermore, all studies were retrospective in nature and carry the inherent disadvantages of any retrospective study. Although most of the studies defined the study population slightly differently there was generally a common theme. Some mentioned the SVS reporting guidelines [87] and clearly their definition was either directly from those guidelines or influenced by them. No study, however, gave detailed anatomical data or used precise anatomical data from pre-operative imaging to define aneurysms with respect to their suitability for endovascular repair or not.

### **6.3.1. Demographic information**

The table below details the pertinent demographic information for the included patients in the selected studies. (See table 6.2.)

**Table 6.2 Demographic Information**

Study	Age, years, mean +/- SD or Median (range)	Male (%)	ASA grade	Pulmonary disease (%)	Coronary artery disease (%)	Preop CKD (%)	Preop Aneurysm Diameter, mean (mm)
Sugimoto, 2018 [123]	72.1 +/- 6.1	85.2	NR	13.9	NR	45.4	55.7
Kabbani, 2014 [124]	71 +/- 7.9	91	NR	37	42	56	66
Speziale, 2010 [125]	71.5 (53 – 85)	93.5	NR	25	41.3	39	53
Knott, 2008 [126]	73.6	78	NR	41	NR	17	62.5
Pearce, 2007 [127]	71 +/- 8	74	III – 68% IV – 28%	33	64	27	59
Sultan, 2011 [128] <sup>a</sup>	70.8 +/- 7.6	77.3	NR	NR	30.3	37.9	66
Deery, 2016 [129] <sup>b</sup>	71 +/- 8	67	NR	41	31	16	61.7
Jeyabalan 2011 [130] <sup>c</sup>	73.2	66.8	NR	NR	63	16.8	60

Table 6.2 – ASA – American Society of Anaesthesiologists, COPD – Chronic Obstructive Pulmonary Disease, CAD – Coronary artery disease, CKD – Chronic Kidney disease, AAA – Abdominal aortic aneurysm. A – Comparing open repair with EVAR, b – Comparing infrarenal and pararenal open aneurysm repair, c – Comparing infrarenal and “complex” open aneurysm repair

There were inconsistencies across the studies about the nature of reporting demographic details. Only one study [127] reported ASA grades for patients and not all studies reported rates of pulmonary or coronary artery disease. Within the reported values there was significant heterogeneity in studied populations also. The proportion of patients who were male varied from 67% - 93.5% across the studies. Furthermore, the reported prevalence of pulmonary disease and coronary artery disease varied widely across the included studies ranging from 13.9 – 41% and 30.3 – 63% respectively. Within the studies there was often little or no detail relating to how pulmonary disease and coronary artery disease were defined despite recommendations in published reporting standards [24]. This may account for the wide variation but is only speculation and again highlights important heterogeneity between the populations. All studies reported rates of chronic kidney disease within the studied populations and again there was relatively wide variation in the prevalence of chronic kidney disease preoperatively ranging between 16 and 56%. It should be noted that studies used a variety of means to define chronic kidney disease. Four studies [126, 127, 129, 130] defined chronic kidney disease as anyone with preoperative creatinine levels of >1.5mg/dL. Two studies [123, 124] used CKD staging criteria with an eGFR of <60 mL/min/1.73 m<sup>2</sup> to define chronic kidney disease. One study [125] defined it as a serum creatinine clearance of <40ml/min and one other study [128] did not report how CKD was defined. The above snapshot of reported patient demographics from each of the included studies highlights the significant heterogeneity between study populations and it is important to bear this in mind when drawing conclusions from this systematic review.

Most studies report preoperative aneurysm diameter to be in the region of 60mm however Speziale et.al. [125] report a mean diameter of 53mm in their study and comment that a 32mm AAA was treated in their series with no explanation given as to why such a small aneurysm was treated.

### 6.3.2. Clamp position and timing

The following table details the information given in each study regarding clamp positions and relative renal/visceral ischaemic times reported. In all cases the clamp position was above at least one renal artery in the studied population. (See table 6.3)

*Table 6.3. Clamp position and timing*

Study	Clamp positions (%)	Total reported Renal/Visceral Ischaemia time, mins (Mean)
<b>Sugimoto, 2018 [123]</b>	Inter-renal 62.9% Suprarenal 31.5% Supraceliac 5.6%	NR
<b>Kabbani, 2014 [124]</b>	Inter-renal 13% Supraceliac 39%	NR
<b>Speziale, 2010 [125]</b>	Inter-renal 27.2% Suprarenal 72.8%	26.7
<b>Knott, 2008[126]</b>	Inter-renal 35% Suprarenal 44% Supra SMA 17% Supraceliac 4%	22.5
<b>Pearce, 2007 [127]</b>	Inter-renal 43% Suprarenal 39% Supra SMA 13% Supraceliac 5%	30 (Median)
<b>Sultan, 2011 [128]<sup>a</sup></b>	Inter-renal 100%	NR
<b>Deery, 2016 [129]<sup>b</sup></b>	NR	24
<b>Jeyabalan2011 [130]<sup>c</sup></b>	Inter-renal 23.9% Suprarenal 55.4% Supra SMA 3% Supraceliac 17.9%	29.7

*Table 6.1 - A – Comparing open repair with EVAR, b – Comparing infrarenal and pararenal open aneurysm repair, c – Comparing infrarenal and “complex” open aneurysm repair*

There is again significant heterogeneity within the selected studies with regards to clamp position with proportion of supraceliac clamping ranging from 0 – 39%. All studies report

a mean or median clamp time of 30 mins or under, but 3 studies did not report the ischaemia time at all. In one study [128] all the clamps were inter-renal, and in another [125] they were all below the SMA. In scrutinising these studies in more detail, it became apparent that strict inclusion criteria applied by the authors led to this finding rather than a specific strategy by the operating surgeons. This therefore indicates significant sampling bias in these studies at least. It appears that this is an attempt by the authors to try and select an anatomically homogenous group for analysis (i.e. to capture juxtarenal but not infrarenal aneurysms) but it is notable that the studies use clamp position as a surrogate marker for anatomy rather than using anatomy itself to define their patient population for study. For the remaining studies the decision at which level the clamp was placed at was driven by surgeon preference, whether this be in relation to specific anatomic features for a given operation or because of a specific strategy. There continues to be debate within the literature at large as to the most appropriate site for placement of an aortic cross clamp with some authors advocating routine supraceliac clamping for juxta and pararenal aneurysms and others citing worse outcomes in terms of morbidity and mortality in this undergoing supraceliac clamping. [131-133] Regardless, within the selected studies, Kabani et al and Knott et. al. investigated but did not find any significant association between clamp site and mortality, however numbers remain relatively small in each study. Two of the included studies did however find a significant association between clamp location and renal outcomes [127, 130] with higher clamp levels relating to higher levels of renal dysfunction in the short term. Again, numbers remain relatively small as with all studies in this systematic review

### 6.3.3. Perioperative Outcomes

The following tables details pertinent perioperative outcomes reported in the included studies (See table 6.4) and perioperative rates of renal dysfunction (See table 6.5)

**Table 6.4. Perioperative Outcomes after Open Surgical Repair of NSA AAA**

Study	Perioperative Mortality (%)	Morbidity – as reported in individual studies	Reintervention (perioperative)
Sugimoto, 2018 [123]	0.9	NR	NR
Kabbani, 2014 [124]	3	Pulmonary 15%	NR
Speziale, 2010 [125]	1.1	"Major complications" 24%	NR
Knott, 2008[126]	0.8	Cardiac 14% Pulmonary 11% Mesenteric ischaemia 2%	NR
Pearce, 2007 [127]	3	Any morbidity 36% Major 23% Cardiac 15% Pulmonary 18%	NR
Sultan, 2011 [128] <sup>a</sup>	4.5	NR	NR
Deery, 2016 [129] <sup>b</sup>	2.7	CHF 7.2%* Pulmonary 19%*	8.4% return to theatre
Jeyabalan2011 [130] <sup>c</sup>	6	NR	Bleeding req re-exploration 4.3% (vs 0.4%) *

Table 6.2 - \* - Statistically significant result when compared with comparator group, NSA – Non-standard Anatomy, AAA –Abdominal aortic aneurysm, CHF – congestive heart failure, NR – not reported. A – Comparing open repair with EVAR, b – Comparing infrarenal and pararenal open aneurysm repair, c – Comparing infrarenal and “complex” open aneurysm repair.

Perioperative mortality was reported in the majority of studies and ranged between 0.8 and 6%. The total combined perioperative mortality for all studies was 37 patients out of 1150 (3.2%). Due to small numbers of perioperative deaths in individual studies only one

[130] with the highest perioperative mortality rate of 6% (11 patients) could perform regression analysis to determine if there were any predictive factors for this outcome. They found that the presence of preoperative coronary artery disease, post-operative myocardial infarction and any post-operative pulmonary complications as a predictor of perioperative mortality. Of note, this was the case for the juxtarenal aneurysm population being studied as well as the infrarenal aneurysm comparator group. The presence of juxtarenal aneurysm, length of renal ischaemia time, left renal vein division or renal insufficiency preoperatively were not predictive of perioperative mortality in that group.

Of the three comparative studies no study found a significant difference between the juxtarenal aneurysm population being studied and their comparator group with regards to perioperative mortality. However, Deery et. Al. did find a significant difference when comparing all “complex AAA” which included type IV thoracoabdominal and suprarenal aneurysms as well as juxta renal aneurysms which had a 30-day mortality rate of 3.6% compared to 1.2% for infrarenal AAA ( $p = 0.002$ ).

Post-operative complications or morbidity was inconsistently reported across studies, but most did report it to some degree. Relatively high rates of “major” morbidity were seen in two studies of 24 and 23% [125, 127]. Only two studies [129, 130] reported on reintervention rates in the immediate post-operative period as detailed in the table.

Deery et. al. found significantly increased rates of congestive heart failure in the pararenal aneurysm group compared with their infrarenal open repair comparator group. That study also found a higher reintervention rate in the NSA group (8.4% vs 5.9%) but this didn't reach statistical significance. Jeyabalan et.al. found in their study that there were a significantly greater proportion of patients requiring re-exploration for bleeding in the “complex”, NSA group compared with the infrarenal SA group.

**Table 6.5. - Perioperative rates of renal dysfunction after Open Surgical Repair of NSA AAA**

Study	Proportion of patients with perioperative Renal dysfunction (%)	New permanent dialysis on discharge (%)
Sugimoto, 2018 [123]	18.7%	0
Kabbani, 2014 [124]	47%	1.5
Speziale, 2010 [125]	11%	0
Knott, 2008[126]	18%	1
Pearce, 2007 [127]	12%	NR
Sultan, 2011 [128] <sup>a</sup>	15.2%*	NR
Deery, 2016 [129] <sup>b</sup>	20%*	1.1%*
Jeyabalan2011 [130] <sup>c</sup>	32.1%*	NR

Table 6.3. - \* - Statistically significant result when compared with comparator group, NSA – Non-standard Anatomy, AAA –Abdominal aortic aneurysm, CHF – congestive heart failure, NR – not reported. A – Comparing open repair with EVAR, b – Comparing infrarenal and pararenal open aneurysm repair, c – Comparing infrarenal and “complex” open aneurysm repair.

The rate of perioperative renal dysfunction varied between studies from 11 – 47%. Some studies clarified that the majority of perioperative renal dysfunction was temporary and had resolved by the time of discharge according to biochemical markers [123, 124, 126]. Rates of new permanent dialysis on discharge were low across the studies included with a maximum incidence of 1.5% [124].

The three comparative studies each independently showed a significant increase in post-operative renal dysfunction in the juxtarenal aneurysm group compared with their endovascular (EVAR) counterparts [128] or infrarenal aneurysm repair comparators [129, 130]. Again, Deery et. Al. also showed significant more rates of new dialysis at the time of

discharge compared to the infrarenal repair comparator group in that study (1.1% vs 0.5% respectively).

#### **6.3.4. Primary Outcome Measures**

The primary outcome measures for this systematic review were: perioperative mortality from any cause (discussed above), all-cause mortality, aneurysm related mortality and reintervention rates. The mean or median follow up was not reported within two studies [124, 129] and ranged between 12 – 54 months in the remaining studies. All-cause mortality over long term follow up was not reported in two of the studies [124, 130]. For the remaining studies 5-year survival rates were given in four of them [125-127, 129] and ranged from 64% - 88.6%. Knott et al. also noted that the 5-year survival rate by Kaplan Meier analysis of 64% did not differ when compared with a general age and gender matched population. Sultan et. Al. who compared open surgical repair with endovascular aneurysm repair did not find any statistically significant difference between the two groups in terms of survival over the longer term with a 3-year survival of 85% for open repair and 57% for EVAR. Despite the disparity in the survival rates there wasn't a statistically significant difference reflecting the limited numbers "at risk" beyond 2 years in that group (less than 20). Deery et al who compared "complex" AAA repair with infrarenal AAA repair also showed no significant difference in survival at 5 years.

Three studies investigated predictors of long-term survival or mortality by regression analysis. [124, 127, 129] As would be expected those studies found that patients with advanced age, pre-existing conditions such as COPD, coronary artery disease or worse preoperative renal function had worse survival outcomes. Kabani et. Al. who investigated outcomes for patients with juxta renal, suprarenal and type IV thoracoabdominal aneurysms did not find that proximal extent of the aneurysm predicted survival over the longer term.

Aneurysm related mortality was not explicitly stated or reported across most studies. Sultan et. Al. who compared 66 open repair patients with 52 patients treated endovascularly noted a statistically significant difference in aneurysm related survival after 3 years with KM estimates of survival for open repair being 92.4% and EVAR 100% ( $p=0.045$ ). Reintervention rates over follow up were similarly poorly reported in the included studies. One non comparative study recorded a rate of reintervention over a median follow up of 32 months as 10% after open repair [127]. No details were given as to the nature of the interventions or timing. Sultan et.al. who compared open and endovascular repair noted a non-significant difference in freedom from reintervention at 3 years: 95.5% for open repair and 83.4% for EVAR ( $p=0.301$ , 95% CI 0.47 to 9.87).

#### 6.3.5. Secondary Outcome Measures

The secondary outcome measures are as follows:

- Primary Technical success
- Clinical success
- Visceral vessel patency
- Length of hospital stay
- Rates of renal dysfunction throughout follow up

Length of hospital stay ranged from 7 – 18.5 days (mean or median) for the included studies. None of the included studies specifically reported primary technical success or clinical success at any point. Similarly, no study reported rates of visceral vessel patency for the whole cohort. One study did comment that 11 out of 13 renal arteries that were revascularized at the time of the original operation were patent on follow up at a mean of 717 days. This was from a total cohort of 126 patients. Perioperative renal dysfunction is detailed above and reported outcomes for renal function over the longer term are reported in the following table (See table 6.6.):

**Table 6.6. – Reported rates of Renal Dysfunction after Open Repair for NSA AAA**

Study	Median Follow up (months)	Proportion of patients with new renal dysfunction during follow up	Documentation of renal protective measures during surgery
Sugimoto, 2018 [123]	34	15.9%	N
Kabbani, 2014 [124]	NR	NR	Y
Speziale, 2010 [125]	54	NR	Y
Knott, 2008[126]	48	NR	Y
Pearce, 2007 [127]	32	24%	N
Sultan, 2011 [128] <sup>a</sup>	33	NR	Y
Deery, 2016 [129] <sup>b</sup>	NR	NR	Y
Jeyabalan2011 [130] <sup>c</sup>	12	5.1%	Y

Table 4.6. - NSA – Non-standard Anatomy, AAA –Abdominal aortic aneurysm, CHF – congestive heart failure, NR – not reported. A – Comparing open repair with EVAR, b – Comparing infrarenal and pararenal open aneurysm repair, c – Comparing infrarenal and “complex” open aneurysm repair.

Although perioperative renal dysfunction was well reported in the included studies longer term renal function was not and varied widely between the three studies that did report it from 5.1% to 15.9%. Furthermore, these studies used varying definitions for what constituted renal dysfunction in the longer term. As such, conclusions about the rate of renal dysfunction after the perioperative period is difficult to make from review of the included studies. Sugimoto et.al. found that the only predictive risk factor for post-operative chronic renal decline in their study was a pre-existing renal dysfunction characterised by stage 3 or 4 using eGFR criteria. Furthermore, they comment that left

renal vein division did not appear to have any causal relationship to renal function post operatively.

#### **6.4. Summary of Results**

In summary there were 8 studies included in the final systematic review with a total population of 1150 patients with NSA treated by open surgical repair. The studies were all retrospective in nature and cohort studies. Three were comparative and five non-comparative. Overall the studies were of poor methodological quality in general and there was significant heterogeneity in study design, definitions (of both aneurysm anatomy and outcome measures), patient populations and operative technique (namely aortic cross clamp level).

The reported perioperative mortality rate ranged from 0.8 – 6%. The 5-year survival rate across four studies which reported this outcome ranged from 64% - 88.6%. It was also noted by Knott et.al. that the 5-year survival rate by Kaplan Meier analysis of 64% did not differ when compared with a general age and gender matched population in the U.S.A.

Aneurysm related mortality and reintervention rates were poorly reported across all studies and as such very limited conclusions can be drawn from these outcome measures.

With regards to the secondary outcome measures investigated again technical and clinical success were not reported at all and rates of renal dysfunction during follow up were rarely reported with significant heterogeneity between studies as to what constituted renal dysfunction. The length of hospital stay ranged between 7 – 18.5 days.

The rate of perioperative renal dysfunction varied between studies from 11 – 47%. For the most part it was noted that this renal dysfunction was transient and had resolved by the time of discharge and that although appreciable the rates of new permanent dialysis on discharge were low across the studies included with a maximum incidence of 1.5% [124].

Of note the three comparative studies found that the rates of postoperative renal dysfunction were significantly higher in the juxtarenal aneurysm cohort compared to either the endovascular cohort [128] or the comparator infrarenal open repair cohort [129, 130].

## 6.5. Discussion

This systematic review attempts to enlighten the discussion about what is considered the gold standard treatment for this particular condition. That is: Juxtarenal abdominal aortic aneurysm, to use the traditional definition reported in most of the literature regarding open repair, or AAA with NSA as proposed in this thesis. The search was limited to the preceding 20 years only primarily to exclude historical reports and include only a “modern” cohort of patients with the presumption that medical and surgical care continues to advance in general and therefore to include more historical reports would incur an important confounding factor. Furthermore, this time limit was chosen as it reflects, approximately, the time period in which endovascular aneurysm repair has become widespread and ultimately the aim is to enable comparison between open repair and endovascular repair of aneurysms with NSA. It was hypothesised before the beginning of the systematic review that more recent studies pertaining to open surgical repair would consider the reporting standards and norms within endovascular research when designing, conducting and disseminating research on open repair. So that certain outcome measures (such as aneurysm related mortality) and definitions (CT based precise anatomical definitions pertaining to the aneurysm neck) would be common in both open surgical and endovascular research and allow robust comparisons between the two. However, the included studies did not, in general, exhibit such an alignment with endovascular reporting standards and as such make comparisons difficult. As an example, the definition with regards to anatomy of the aneurysm was based either on clamp level intraoperatively on the SVS definition of juxtarenal aneurysm. There was no specific assessment of aortic neck

anatomy from the preoperative CT scan as would be expected in any report pertaining to endovascular repair. There is therefore inevitable heterogeneity in the anatomy of the populations being studied limiting comparisons that can be made. It is the recommendation of this author that future such studies whether comparative or not into open surgical repair of aneurysms should define anatomy precisely and based on preoperative CT analysis, which with the advent of computerised radiology software which is now commonplace in all hospitals in the United Kingdom and beyond, should be possible to achieve. Furthermore the use of reporting standards published for endovascular aneurysm repair but with comment on open repair [24] should be used to inform the method of reporting.

None of the studies identified and analysed included ruptured aneurysms but three studies [126, 127, 129] commented that symptomatic/urgent aneurysms were included in their study cohort. The proportion was 9.5%, 11% and 11% in the three studies. The remaining studies did not make an explicit statement that symptomatic aneurysms were excluded but, in some cases, commented that only elective aneurysms were included.

Sultan et.al. compared open aneurysm repair with patients treated by endovascular repair for NSA. In addition to the above reported outcomes they also interestingly comment that the number of patients discharged home rather than to another healthcare facility was significantly higher after EVAR than open repair (90% versus 70%,  $p=0.006$ ). They also undertake cost effective analysis and find that in their study the mean cost per patient over a 3-year period is higher for open repair than for EVAR by approximately €3500. It appears the main source for this extra cost is in the extended length of stay in hospital and on ICU and longer operating time. It should be noted that these were standard endovascular grafts and if comparing with advanced endovascular techniques the extra cost of the

endovascular device may negate some or all of that cost burden from open repair in comparison.

Various renal protective strategies are commented upon in the included reports however there is little that can be said about their efficacy due to lack of comparator groups/analysis into their effectiveness. Strategies used include the use of N-acetylcysteine, mannitol, furosemide, bicarbonate and the use of cold renal perfusion during the operation.

## **6.6. Conclusion**

Very limited information can be drawn from this systematic review due to the poor methodological quality of the studies and the heterogeneity evident between them. Nevertheless, it serves to provide data specifically about the rate of specific clinical outcome measures such as perioperative mortality, across the literature to enable some comment or comparison with other treatment options. This systematic review also highlights, importantly, the lack of standardised reporting for open aneurysm repair and though it is beyond the scope of the current work suggests an important area for future work – Combined open/endovascular reporting standards.

## **7. CHAPTER 7 - Systematic Review of Clinical outcomes Following Fenestrated Endovascular Aneurysm Repair**

### **7.1. Introduction**

In conjunction with the systematic reviews outlined above this final systematic review aims to provide an updated synthesis of the available evidence from previously conducted systematic reviews and meta-analyses and contemporaneous reports investigating specifically the clinical outcomes for aneurysms undergoing fenestrated endovascular aneurysm repair.

From the previous systematic reviews, it became clear that there is a broad base of published literature regarding fenestrated endovascular repair and a plethora of systematic reviews and meta analyses published since the advent and widespread use of fEVAR. It was therefore decided to synthesise the available evidence across the available systematic reviews and meta-analyses published to date, and then perform a systematic review of articles published since the most recent systematic review.

The question being addressed in this systematic review is to understand what the clinical outcomes are for patients undergoing fEVAR. The primary clinical outcome measures will include the following both perioperatively and throughout follow up; all-cause mortality, aneurysm related mortality, reintervention rates and graft related endoleaks. Secondary outcome measures will include: primary and primary assisted technical success, visceral vessel patency, rates of conversion to open repair, rates of renal dysfunction and aneurysm expansion throughout follow up.

After Park et al. [79] first reported the use of a fenestrated endovascular stent-graft in 1996 for repair of abdominal aortic aneurysm the principle of endovascular stenting while preserving blood flow to targeted visceral vessels was established. In 1999 two further

reports of experimental placement of fenestrated stent-grafts in canine subjects further proved the principle and paved the way for the use of this new technology. [134, 135] In 2000 a case report describing the use of a fenestrated stent-graft in a female patient with a complex mycotic aneurysm within the visceral aorta was described. [136]

In 2001 the first case series of 13 patients treated with customised stent-grafts based on the Zenith system was reported from Australia. [137] In this study procedural success was 100%, with perfusion maintained to 33 target vessels at the end of the procedure and 0% perioperative mortality. The report describes in detail the construction of the endograft and the implantation procedure as well as recommending stenting through fenestrations of the target renal vessels to help maintain visceral vessel patency.

After the above paper from Australia the literature records the uptake in use of fenestrated technology with multiple case series from around the world being reported with short term follow up data. This period also sees publication of papers relating to experimental models on fenestrated technology assessing forces needed to 'pull-out' or distract the stent grafts from their original position. One study details that the forces required to dislodge the fenestrated stent-graft are significantly greater than that for the standard infrarenal stent-graft. [138] From the Cleveland clinic, U.S.A and the Netherlands two case series were reported during this period both documenting 100% procedural success for a combined population of 50 patients and 129 target vessels. [139, 140] Greenberg et al. reported one death (3%) within the perioperative procedure secondary to aspiration pneumonia. Verhoeven et al. reported one target vessel occlusion during the primary procedure, being the only one out of all 129 vessels from both studies. Both studies had a mean follow up of 9 months and reported good outcomes to this time point with only a further two renal arteries noted to be occluded and 4 patients dead from non-aneurysm related causes. These initial case series further prove the feasibility and safety of the technique with good

short-term outcomes during the initial phase of use of fenestrated technology. A further case series from the Cleveland clinic expanding on the above study investigates the renal effects from fEVAR [141]; in this series of 72 patients 24% suffered a renal event; ranging from renal artery stenosis or occlusion to requirement of permanent dialysis (3%). It was found that most renal events occurred within the first month after fEVAR. This was the first study to fully document the concerns regarding renal outcomes after fEVAR.

After the introduction and acceptance of a new technology there is an initial phase of investigation into feasibility and safety of that technology. Following this, clinical series begin to report on the short-term outcomes after use of the technology as documented above. The next inevitable stage is the expansion in use of the technology with reports on clinical outcomes over a longer follow up period and the publication of systematic reviews of the available evidence. The aim of this systematic review was to synthesise the available evidence by identifying all published systematic reviews on this subject and relevant published articles not included in the latest systematic review.

## **7.2. Methods**

The systematic review followed reporting guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) document. [108] In line with these guidelines a protocol for the systematic review was established prior to the beginning of the literature search as follows. The protocol is reproduced here in its entirety.

### **7.2.1. Protocol for Systematic Review, Including Eligibility Criteria**

A systematic review of the literature will be undertaken to examine the clinical outcomes for patients undergoing abdominal aortic aneurysm repair using fenestrated endovascular aneurysm repair. It is expected that there will be heterogeneity in the definition of anatomical extent of aneurysms being studied between the various published reviews. The

indications for use for fenestrated endovascular aneurysm repair using the Cook Zenith system (Cook Medical, Bloomington, Indiana, U.S.A.) specify that there must be 4mm of infrarenal neck available. Despite this fenestrated technology can be used to treat aneurysms extending up to and even above the renal arteries. Furthermore, branched endovascular technology is recommended for use in, and indeed is used, for aneurysm with this proximal extent also. There is therefore an overlap between fEVAR and bEVAR in terms of the anatomy that they are used to treat. It is expected that there will be heterogeneity and lack of precise definition of aneurysm extent within the published literature. The Ad Hoc Committee on Reporting Standards for the Society of Vascular Surgery [24] use the terms “juxtarenal” and “pararenal” to describe aneurysmal extent, and that the two terms can be used interchangeably. This definition states that there is “no normal aorta between the upper extent of the aneurysm and the renal arteries”. Those reporting standards make a distinction between juxtarenal/pararenal aneurysms and “suprarenal” aneurysms – the latter definition states that the aneurysm segment involves at least the renal arteries if not the splanchnic arteries also. Aneurysms that require branched endovascular technology by definition include suprarenal aneurysms, and aneurysms defined as suprarenal are by definition outside the instruction for use specified for Cook Zenith fenestrated platform. Therefore, aneurysms defined as suprarenal or in which branched endovascular technology is used will be excluded from this analysis. There may be reports that combine the data for branched and fenestrated repair and if so, they will only be included in this analysis if the outcomes can be separated and there is a specific comment that the aneurysms treated by fenestrated repair are juxtarenal or pararenal aneurysms. Ideally all reports would specify anatomic extent of aneurysms by reporting neck lengths and other anatomical features within study populations, however this is likely not to be the case. For practical purposes therefore, the statement that an aneurysm is juxtarenal or pararenal will be sufficient to include it in this analysis. Furthermore, aneurysms described as type IV thoracoabdominal

aneurysms will not be included. The caveat to this is if an aneurysm is defined as suprarenal but specific anatomic criteria are reported to clarify that actually fenestrated endovascular repair could be performed within its IFU.

The objective of the systematic review is to compare the published literature for all patients with non-standard aneurysms undergoing fEVAR. It is expected that no randomised controlled trials would be identified and therefore all systematic reviews, meta-analyses and non-randomised studies published since the most recent systematic review will be included in the analysis.

Inclusion criteria:

- Aneurysm morphology - For a study to be included in the analysis, it should clearly state that the population had morphologic infrarenal neck characteristics that were not within the indications for use for standard EVAR but were within the IFU for fEVAR. As already stated above other definitions will be accepted in line with published reporting standards – such as juxtarenal or pararenal aneurysms as a definition.
- There must be median (or mean) follow up of at least 1 year to enable meaningful results of short and mid-term data for the studied population
- In order to reduce bias introduced from small case series studies must have at least 50 patients undergoing fEVAR

Exclusion Criteria:

- Studies reporting solely on symptomatic or ruptured aneurysms. If a study includes symptomatic or ruptured aneurysms it is expected that the results for these patients will be identifiable and be able to be excluded from further analysis. If it is not possible to do so then an explicit statement as such will be made in the report

to make it clear that this confounding variable exists in the identified study population.

- If the report presents patients treated with a hybrid (endovascular combined with open surgical repair) technique.
- Aneurysms repaired by branched endovascular technology will be excluded from the analysis
- No statement of aneurysm morphology

#### Eligibility Criteria

- Publication dates within 20-year period (1998 – 2018)
- English language only results considered
- The population will include all adults with no age restriction

The above protocol was referred to throughout the data identification and extraction phase to ensure it was adhered to.

#### **7.2.2. Definitions and Outcome Criteria.**

Outcome criteria and definitions were based on recommended reporting standards for EVAR, published by the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery [24]. The outcomes within the first 30 days after the index procedure or occurring within the same hospital admission will be reported as perioperative outcomes, those occurring between 30 days and 1 year will be termed 'Early', those between 1 and 5 years will be termed 'Short', 5 to 10 years will be considered 'Midterm' and > 10 years will be 'Long-term'. This is in line with the pragmatic minimum reporting standards for endovascular aneurysm repair [99]. Primary outcome measures included perioperative mortality from any cause, all-cause mortality, aneurysm related mortality, reintervention

rates and graft related endoleak rates (All type I and III endoleaks). The secondary outcome measures are as follows:

- Primary Technical success
- Visceral vessel patency
- Conversion to open repair
- Rates of renal dysfunction throughout follow up (the definition used within the given study for renal dysfunction will be used)
- Rates of spinal cord ischaemia
- Aneurysm growth throughout follow up (At all time points)

### **7.2.3. Information Sources and Electronic Search Strategy**

An electronic search of the literature was undertaken. The search was applied to MEDLINE (database provider PubMed, from 1998 – 2018) and EMBASE (database provider Ovid, from 1998 to 2018). The search was undertaken once in May 2018. A full record of the search strategy is included within Appendix 3. The full reference list of each full text study assessed was interrogated to identify any relevant articles missed in the original search.

### **7.2.4. Study Screening and Selection**

The study screening and selection strategy employed was exactly that as for the systematic review of clinical outcomes of non-standard aneurysms treated by EVAR (Chapter 5). The search strategy results and reasons for exclusion are listed in figure 7.1 below.

Figure 7.1 - Search strategy for Systematic Review of fEVAR

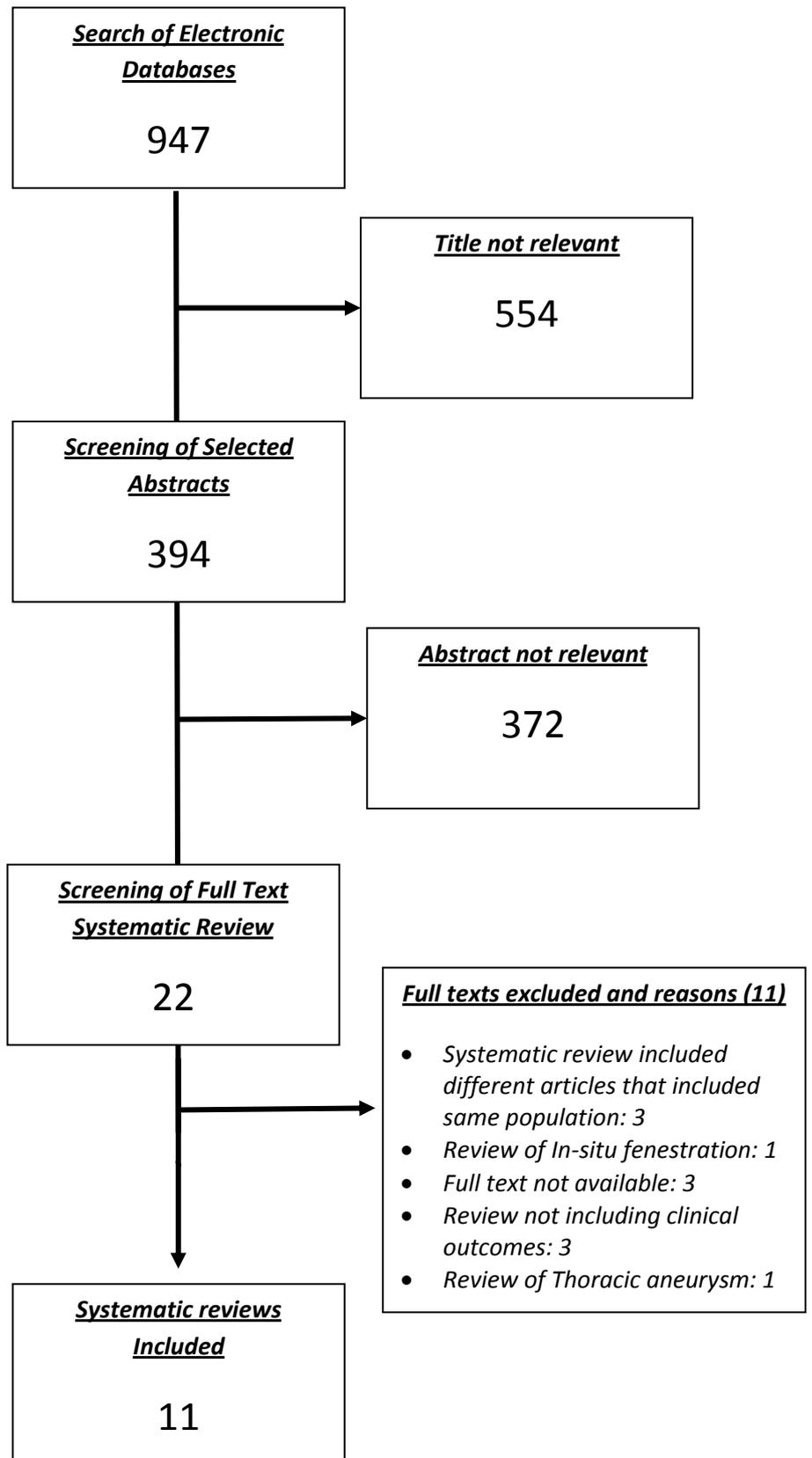


Figure 7.1 - Numbers represent articles. Arrows denote whether articles were excluded or included.

Following this the original list of retrieved articles was then searched again to identify all articles published after the most recent systematic review. The year of the most recent published article included in any systematic review was 2015. Then all published articles from 2015 onwards were screened again. As above the abstracts and then full texts (if appropriate) were reviewed to identify if they should be included in the review or not. After abstract review of all the articles 27 full texts were identified for further review and scrutiny. From this list of 27 articles 8 were included in the final review. The reasons for exclusion of the 19 articles were as follows: 6 articles didn't separate differing anatomies or treatments to allow analysis of fEVAR, four articles did not investigate clinical outcomes of interest, two articles had less than 50 patients undergoing fEVAR, three articles only reported 30 day clinical outcomes, two articles were early reports of a population that were updated in later articles (both updated articles were included), one article was a conference abstract only and was not able to obtain one article.

#### **7.2.5. Data collection**

A data extraction sheet was developed. As well as pertinent information relating to the publication (year of publication, journal etc) the remaining collected variables were divided in three broad categories: (1) baseline clinical and demographic data, anatomic characteristics, and procedure related characteristics; (2) primary outcome data (3) secondary outcome data, as outlined previously.

### **7.3. Results of Systematic Reviews Identified**

After screening 11 systematic reviews were identified throughout the search. These systematic reviews were published between 2006 and 2018. The articles included within the systematic reviews were published between 2001 and 2015 and the number of fEVAR cases included in the systematic reviews ranged between 293 and 776. Five of the articles included a meta-analysis as part of the article and four reviews were comparative in nature

(three comparing with open repair and one with chimney EVAR). The following table outlines the details of the included studies (see table 7.1.)

**Table 7.1 Included systematic reviews of fEVAR**

<b>Author, year</b>	<b>Years of publication of included articles</b>	<b>Number of included articles</b>	<b>Comparative study (Y or N)</b>	<b>Meta-analysis (Y or N)</b>	<b>N of cases</b>	<b>Mean number of target vessels per patient (S.D.)</b>
<b>Spanos, 2018 [142]</b>	2001 - 2015	7	N	Y	772	2.74 (0.77)
<b>Li, 2016 [143]</b>	2005-2013	9	Y (chEVAR)	N	542	2.73 (0.76)*
<b>Rao, 2015 [144]</b>	2005 - 2012	14	Y (OR)	Y	751	2.49 (0.82)*
<b>Ou, 2015 [145]</b>	2006 - 2014	15	N	N	763	2.59 (0.78)*
<b>Belczak, 2014 [146]</b>	2006 - 2012	4	Y (OR)	N	293	2.63 (0.64)*
<b>Di, 2013 [92]</b>	2006 - 2011	12	N	Y	776	2.52 (0.77)*
<b>Linsen, 2012 [147]</b>	2006 - 2011	9	N	Y	629	2.52 (0.77)*
<b>Donas, 2012 [148]</b>	2001 - 2012	12	N	N	631	2.52 (0.78)*
<b>Cross, 2012 [149]</b>	2001 - 2011	11	N	Y	660	2.52 (0.78)*
<b>Nordon, 2009 [150]</b>	2001 - 2008	8	Y (OR)	N	368	2.37 (0.82)*
<b>Sun, 2006 [151]</b>	2001 - 2006	6	N	N	317	2.37 (0.82)*

Table 5.1. \* - Not all studies in systematic review had sufficient information to calculate mean TV ratio and S.D, so result is calculated from studies where that information is present

As can be seen from the above table the mean target vessels per patient increased as time passed - from 2.37 in 2006 to 2.74 in 2015. This suggests that over the past two decades there has been increasing complexity of the fEVAR devices implanted and reported on, with more target vessels incorporated into the treatment. It should also be noted the vast majority of cases reported in the literature are regarding the Cook Zenith platform of fenestrated stent graft, though there are occasional reports of other manufacturers of fenestrated stent grafts. The primary other stent graft within the literature is the Anaconda stent graft.

The four most recently published systematic reviews reports on 27 different studies between them with studies ranging in size from 8 cases of fEVAR to 318 and publication dates ranging from 2001 – 2015. One of these studies [142] present their results with the aim of presenting the “long term” outcomes of fEVAR. Two others compare fEVAR with open repair [144] and chimney EVAR techniques [143]. The following table details the baseline demographic and anatomical factors reported for those four systematic reviews:

(See table 7.2)

**Table 7.2. Demographic Details from Four Most Recent Systematic Reviews**

<b>Author, year</b>	<b>Mean Age (years)</b>	<b>Male patients (%)</b>	<b>AAA diameter (mm), Mean</b>	<b>Neck Length (mm), Mean</b>
<b>Spanos, 2018 [142]</b>	71.5 - 74	86.7%	60 – 65*	NR
<b>Li, 2016 [143]</b>	74	85.7%	64	6.7 (0-14mm) <sup>a</sup>
<b>Rao, 2015 [144]</b>	73	86%	60	NR
<b>Ou, 2015 [145]</b>	72 - 75.5	NR	NR	NR

Table 7.2 - \*- range of mean diameters, a – Mean neck length found in five of 15 studies, range of neck length in parentheses

Within the systematic reviews and all published literature, the vast majority of patients are male (approximately 85 – 87%) and the mean age is between 70 – 75. Mean aneurysm diameter is also relatively constant across the systematic reviews being between 60- and 65-mm. Neck length is poorly reported in the literature and consequently the systematic reviews but Li et.al. report that in five of the fifteen studies included in their systematic review a comment about neck length was made. For these studies the combined mean neck length was 6.7mm (range 0 – 14mm).

It should be noted that there is heterogeneity in the definitions used for comorbidities within the literature. Therefore, it is difficult to compare between studies the rates of any given comorbidity. Furthermore, a significant proportion of studies do not define what constitutes a certain comorbidity. They simply state the proportion of patients with chronic kidney disease (as an example). For the four systematic reviews mentioned above the rates of reported coronary artery disease/ischaemic heart disease range from 33.1% - 52.2%. Hypertension ranges from 67 – 76.8%, diabetes mellitus 15.4 – 17.4%, chronic kidney disease: 18.6 – 27% and respiratory disease: 33.7 – 36%. One study [143] comments that the use and reporting of ASA grading within the published literature is very sparse. The use of other comorbidity scoring systems is occasionally used [24] but again it is infrequently used.

The studies included in the systematic reviews consistently reported high technical success rates of the procedures with successful introduction of the stent graft and high visceral vessel patency at the end of the procedure. The target vessel patency rates at completion angiogram were in the region of 90% [83] to 100% [152-154]. Semmens et al. [83] commented that one factor associated with target vessel loss in the short term was a lack of stenting through a fenestration for targeted renal vessels. One study also noted that

when target vessel occlusion did occur, they tended to be within the first year after the operation [155].

Significant heterogeneity was seen between the reporting practices of the systematic reviews pertaining to which clinical outcomes measures were included and in what form. The following table details the results across the systematic reviews for various important clinical outcome measures as reported within the systematic reviews. (see table 7.3)

**Table 7.3 Outcome Measures within systematic reviews of fEVAR**

<b>Author, year</b>	<b>Periop Mortality</b>	<b>Range of Follow up periods for studies included ,months</b>	<b>All-Cause Mortality through FU</b>	<b>TV Patency through FU</b>	<b>Graft Related Endoleak through FU</b>	<b>Reintervention Rate through FU</b>
<b>Spanos, 2018 [142]</b>	2.5%	6 - 67	40%	86.8%	NR	24%
<b>Li, 2016 [143]</b>	1.1%	12.8* (1 – 65)	5.4%	95.9%	NR	10.7%
<b>Rao, 2015 [144]</b>	4.1%	-	45%	95.8%	2.2%	12.7%
<b>Ou, 2015 [145]</b>	1.7%	11 - 67	20.1%	96.4%	NR	30%
<b>Belczak, 2014 [146]</b>	0 -2%	21* (13- 24)	NR	NR	NR	NR
<b>Di, 2013 [92]</b>	2.5%	15 - 25	NR	94.5%	NR	17.6%
<b>Linsen, 2012</b>	2.1%	15 - 27	16%	93.2%	NR	17.8%

[147]						
<b>Donas, 2012</b> [148]	1.2%	-	NR	NR	NR	NR
<b>Cross, 2012</b> [149]	2%	24*	NR	NR	NR	NR
<b>Nordon, 2009</b> [150]	1.4%	-	NR	NR	NR	NR
<b>Sun, 2006</b> [151]	1.1%	6 – 25	8.3%	90%	9.4%	NR

Table 7.3. – FU – Follow up, TV – target vessel, NR – Not reported \* - Mean follow up across all included studies

Therefore, the perioperative mortality reported in the systematic reviews ranges from 0 – 4.1%. With most reporting between 1 and 2% perioperative mortality rates. The majority of studies within the literature report mean or median follow ups that are within approximately 2 years. It is difficult to compare long term mortality between studies and systematic reviews because of the differing reporting practices and follow up times between studies and reviews however one systematic review by Spanos et.al. attempts to present longer term dates. They report results from seven studies that all have follow up ranges that exceed 36 months. The details of pooled estimated mortality rates (with 95% CI in parentheses) over the longer term in their review is as follows:

- 12 months: 0.080 (0.060-0.106)
- 24 months: 0.129 (0.097- 0.169)
- 36 Months: 0.211 (0.158-0.277)
- 48 Months: 0.279 (0.193-0.386)
- 60 Months: 0.405 (0.303-0.517)

They have therefore, shown a mortality rate of approximately 40% at 5 years. Aneurysm related mortality over follow up is generally poorly reported in the literature. There is rarely as estimation of aneurysm mortality free survival by Kaplan Meier analysis reported which would be the most accurate way to present such data. Studies may report rates of aneurysm related mortality as a percentage of all patients included, all patients surviving beyond 30days or as a proportion of late follow up deaths. It is the opinion of this author that these methods are misleading and do not give a true representation of aneurysm mortality free survival. Nevertheless, the numbers of patients identified as having an “aneurysm related” mortality within the literature during longer term follow up remain small.

The four most recent systematic reviews, detailed above, were interrogated to ascertain perioperative and longer-term rates of reintervention and graft related endoleak. For perioperative reintervention; Spanos et. al. reports a pooled estimated perioperative reintervention rate of 5.9% (4- 8.8%) within their systematic review. That same systematic review also reports the following reintervention rates as pooled estimates over the longer term:

- 12 months: 0.097 (0.066-0.140)
- 24 months: 0.131 (0.082-0.203)
- 36 Months: 0.281 (0.182-0.406)
- 48 Months: 0.244 (0.103-0.477)

Li et. al. reports a combined reintervention rate over follow up in their systematic review of 9 articles with a median follow up of 12.8 months as 10.7%. Rao et. al. Also show a pooled estimated reintervention rate of 12.7% for their 14 included studies.

The rates of perioperative (either at completion angiography or within first 30 days) graft related endoleak are reported in three reviews for type 1 endoleak [142-144] and two reviews for type 3 endoleak [142, 144]:

- Perioperative Type 1 endoleak rate – 3.7%, 5.8% and 5.8%.
- Perioperative type 3 endoleak rate – 1.6% and 2.6%.

Graft related endoleak was infrequently reported within the systematic reviews during longer term follow up primarily because of heterogeneity between included studies for their length of follow up and therefore cannot be commented on here.

It should be noted that only one article that was frequently cited in the systematic reviews, Kristmundsson et al. [84], has a median follow up that could be classified as mid-term (>5 years). In that paper, overall survival at 5 years was noted to be 60% with the majority of deaths secondary to non-aneurysm related causes. During follow up there were no conversions to open repair and only one patient died of aneurysm rupture secondary to component separation and endoleak. The primary target vessel patency at 5 years was 90% and primary assisted patency was 93%. Eight target vessels occluded throughout follow up (three SMAs and five renal arteries), only one of the renal artery patients suffered any clinical consequence from their occlusion – they became dialysis dependant. The reports on long term follow up after fEVAR are, at this point, relatively scarce, however they do appear to show continued efficacy of the technique in terms of avoiding aneurysm rupture without major adverse event in the long term.

Since the proliferation of fEVAR there have always been concerns about the fate of target vessels and the outcomes for patients in terms of the incorporated visceral vessels. A report by Grimme et al. [156] has investigated this concern in 138 patients who received fEVAR over a ten-year period. There were 392 target vessels, 140 of which were protected

by a scallop and 252 with fenestrations. A variety of stents were placed in 254 target vessels. Overall patency rates for visceral artery stents was 88.6% at four years in that study. They noted that stent fractures and renal artery stenosis occurred more frequently in uncovered stents. This study confirms with the remaining body of evidence that outcomes after fEVAR for visceral vessels are good and that even when target vessel events do occur it does not necessarily lead to disastrous clinical consequences such as dialysis or frank bowel ischaemia resulting in death or need for operation.

#### **7.4. Results of Original Articles Identified from Systematic Review**

As stated above 8 articles were identified [157-164] using the inclusion and exclusion criteria from the literature from the beginning of 2015 onwards. Four of these articles [157-160] were updates from centres that had previous published reports which were included in some of the systematic reviews reported above. The following table documents the studies included from this portion of the systematic review: (See table 7.4)

**Table 7.4. Details of original studies investigating fEVAR published since 2015**

<b>Author, year</b>	<b>Years patients treated</b>	<b>N</b>	<b>Mean number of target vessels per patient (S.D)</b>	<b>Type of study</b>	<b>Follow up of study, mean or median with S.D. or range (months)</b>
<b>Verhoeven, 2016 [157]</b>	2010 - 2014	281	3.19 (0.48)	Single centre, retrospective	21 +/- 15.9
<b>Oikonomou, 2017 [158]</b>	2006 - 2014	141	3.64*	Single centre, retrospective	33 +/-23
<b>Blankensteijn, 2017 [159]</b>	2011 - 2015	60	2.33 (0.73)	Multi centre, retrospective	16.4 (11.9 - 27.4)
<b>Roy, 2017 [160]</b>	2003 - 2015	173	3.31 (0.77)	Single centre, retrospective	34
<b>deSouza, 2017 [161]</b>	2005 - 2012	67	NR	Matched cohort study from US multicentre trial	32
<b>Caradu, 2017 [162]</b>	2010 - 2015	90	2.2 (0.5)	Single centre, retrospective	19 (1 - 68)
<b>Wang, 2018 [163]</b>	2012 - 2017	100	NR	Single centre, retrospective	20.4
<b>Colgan, 2018 [164]</b>	2010 - 2014	101	3.08 (0.76)	Multi centre, retrospective	12

**Table 7.4. S.D. – Standard deviation, NR – Not reported- \* Data not given to allow calculation of S.D.**

As can be seen the majority of these contemporaneous reports include more complex stent graft designs with a higher number of target vessels per patient (>3) when compared with the systematic reviews outlined above. All of these studies only included outcomes for fenestrated endovascular repair without combining results for branched endovascular repair in line with the inclusion and exclusion criteria for this systematic review.

Furthermore, three studies [157, 158, 160] specifically state that thoracoabdominal, or type 4 aneurysms were excluded from their analysis. This represents a shift compared to the previous period from when the systematic reviews were drawn where often reports may include these aneurysms or combine branched and fenestrated outcome data. The majority of the above studies report outcomes for the Cook Zenith fenestrated platform with the notable exception of two: Blakensteijn et.al. and Colgan et.al. document their centres' experience with the use of the Anaconda stent-graft.

The largest study found during the literature search was a report by Gupta et.al. [165] with 535 patients. They used the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to capture patients. This is essentially a large registry dataset from numerous hospitals across the United States that collects data prospectively. In that study they only examined 30-day outcomes and therefore it was excluded from this analysis, but it merits mention because of the large number of patients.

#### **7.4.1. Demographic Details**

The table below documents the demographic and anatomical details recorded in the included studies: (See table 7.5)

**Table 7.5. – Demographic details within original studies investigating fEVAR published since 2015**

<b>Author, year</b>	<b>Age, years mean or median (With S.D.)</b>	<b>Male (%)</b>	<b>AAA diameter, mm (mean or median with S.D. or range)</b>	<b>Aneurysm neck length, mm (mean or median With S.D. or range)</b>
<b>Verhoeven, 2016 [157]</b>	72.1	87%	60.2 (45 - 110)	2 (0 - 10)
<b>Oikonomou, 2017 [158]</b>	72 (7.6)	85%	-	NR
<b>Blankensteij m, 2017 [159]</b>	72 (7)	86.7%	64 (9)	6 (4)
<b>Roy, 2017 [160]</b>	76	90%	63	NR
<b>deSouza, 2017 [161]</b>	74	81%	60	NR
<b>Caradu, 2017 [162]</b>	71.3 (6.6)	98%	58.3 (9.8)	NR
<b>Wang, 2018 [163]</b>	72.6	86%	NR	NR
<b>Colgan, 2018 [164]</b>	76	85%	64 (45 - 106)	5 (1 - 13)

**Table 7.5. AAA – Abdominal aortic aneurysm, S.D. – Standard deviation, NR – Not reported- \* Data not given to allow calculation of S.D.**

As with the systematic reviews reported above the age and gender of the population being studied is fairly similar. The reporting of specific anatomical characteristics such as neck length are more common place in these included studies and suggests a relatively heterogenous group of aneurysms being treated with a median neck length of 2mm in one study compared to 6mm in another. (Although there are still only three studies from 8 that do report the neck length)

Comorbidities were reported using varying definitions across the studies, so it is difficult to compare patient populations accurately across the studies but for completeness the reported rates are given here: (See table 7.6.)

**Table 7.6. - Comorbidities within original studies investigating fEVAR published since 2015**

Author, year published	CAD (%)	HTN (%)	Resp Disease (%)	CKD (%)	Definition of CKD used	Previous aneurysm repair (%)	ASA grade (3 or more) (%)
Verhoeven, 2016 [157]	59.8	78.3	48.8	44.5	Cr >100 µmol/L	16	39.1
Oikonomou, 2017 [158]	70	95%	52	41	GFR <60	25	68
Blankensteijn, 2017 [159]	55	65	26.7	28.3	NR	-	63.3
Roy, 2017 [160]	52.6	63.6	NR	57.8	NR	8.7	69.7
deSouza, 2017 [161]	16	90	36	24	NR	-	-
Caradu, 2017 [162]	43.3	80	26.7	14.4	NR	3.3	-
Wang, 2018 [163]	50	89	36	16	Cr >1.5 mg/dL	12	-
Colgan, 2018 [164]	52	71	NR	39	Stage 3 or more	2	76

Table 7.6. AAA – Abdominal aortic aneurysm, S.D. – Standard deviation, NR – Not reported, CAD – coronary artery disease, HTN – Hypertension, CKD – Chronic kidney disease, ASA – American society of anaesthesiologists, Cr – Creatinine.

There was significant heterogeneity among the reported studies with regards to preoperative renal dysfunction as can be seen from the table above, but this is partially explained by the differing definitions used for CKD. The study by Verhoeven et.al. is notable

in that only 39.1% of patients had an ASA grade of 3 or more but the authors state in their study that they use fEVAR as a first line treatment for suitable patients and do not reserve it for those unfit or at “high risk” or open repair as stated in most other studies. Despite this however their patients still commonly exhibit coronary artery disease, chronic kidney disease, hypertension and respiratory disease. This probably reflects the fact that proportions of comorbidities seen in a population do not accurately reflect the “fitness” of a given population well. Nevertheless, these factors are commonly reported to allow comparisons between populations to be drawn.

#### **7.4.2. Perioperative Outcomes**

The perioperative technical success was reported in six studies. Four of these studies [157, 158, 162, 163] report technical success rates of between 95.7 – 98%. This is in keeping with most previous reports for fenestrated repair. The other two studies report a technical success rate of 79.2% [160] and 85% [159]. Both these studies importantly however comment that this low rate is primarily secondary to intraoperative endoleaks that spontaneously sealed by the time of the first post-operative imaging. When adjusting for this Roy et.al. report a technical success rate of 95.4%.

Perioperative mortality ranges from 0.7 – 5.2% in the included studies. The exceptionally low rate of 0.7% was seen in the study by Verhoeven et. al. mentioned above in which fEVAR was used as a first line treatment option. The highest rate of 5.2% was seen in the study by Roy et.al. where the authors offer the explanation of more complex graft design used in their study to account for the higher perioperative mortality rate. Of all the studies they did have the highest mean number of target vessel per patient in their study with 3.3. The pooled mortality rate for all the included studies was: 2.7%. Excluding the study by Verhoeven et. al. with the low mortality rate the perioperative mortality for the remaining

studies was 3.4%. Of note the perioperative mortality rate in the study mentioned above by Gupta et.al. of 535 patients, [165] which was not included in the final analysis, was 2.4%.

Three studies reported proportions of type 1 endoleak at completion angiogram:

- 11.7% - all resolved without intervention [159]
- 2.2% [162]
- 11% - 11 patients, 10 resolved without intervention, one required further angioplasty which resolved endoleak [164]

The same three studies also reported type 3 endoleaks:

- 3.3% - all resolved
- 3.3%
- 4%

Perioperative open conversion was specifically reported in five studies, with 3 patients out of 756 (0.4%) suffering this complication. Presumably in the other studies it was not mentioned as it didn't happen, and if this is true then the true rate of perioperative conversion in this systematic review is 0.3%.

The following table documents the rates of renal insufficiency (as defined in each study), spinal cord ischaemia, and "complications" in the perioperative period. (See table7.7.)

**Table 7.7. Perioperative outcomes from included studies**

Author, year published	Renal Insufficiency	Spinal cord Ischaemia	Complications
Verhoeven, 2016 [157]	5% AKI	NR	12.1%
Oikonomou, 2017 [158]	2.1% AKI	2.8%	12.1%
Blankensteijn, 2017 [159]	30% Renal dysfunction	NR	25%
Roy, 2017 [160]	27.8% AKI	1.1%	27.2%
deSouza, 2017 [161]	5% AKI	NR	NR
Caradu, 2017 [162]	17.8% AKI	NR	NR
Wang, 2018 [163]	NR	1%	5%*
Colgan, 2018 [164]	3% AKI	0%	16%

Table 7.7. – AKI – acute kidney injury NR – Not reported, \* “cardiovascular” complications only.

Spinal cord ischaemia was specifically mentioned in 4 studies as above. Seven patients (1.4%) suffered spinal cord ischaemia. It was noted to be transient in all with spinal protective measures (spinal cord drainage and blood pressure control) used in all cases, either prophylactically or as a reaction to the complication. In four cases a spinal drain was only placed after discovery of the symptoms, in two cases a spinal drain had been placed preoperatively but one developed symptoms after clamping of the drain and the other had symptoms related to hypotension which resolved after improving the blood pressure. In the other case the details are not mentioned in the report.

The rate of post-operative complications ranged from 12 – 27%. In five studies a detailed breakdown of complications in the post-operative period was given to enable the following summary [157-160, 164]:

Of 756 patients in those five studies 127 (16.8%) were documented as having had a “post-operative complication”. The complications were as follows:

- Renal dysfunction 29 patients
- Cardiac complications 21 patients
- Respiratory 18 patients
- Access related complications (Including bleeding needing return to theatre and conservatively managed seroma) 28 patients
- Stroke 2 patients
- Mesenteric ischaemia (Including operated and conservatively managed) 7 patients
- Wound infection 10 patients
- Other 12 patients

Studies varied in their definition of complications however and some only reported those that “prolonged hospital stay” [160] whereas most did not specify what qualified as a post-operative complication.

### 7.4.3. Longer term Outcomes

Overall survival was reported in the majority of the studies and is detailed in the table below for varying time points: (see table 7.8)

**Table 7.8 – Overall survival for fEVAR patients from Included Studies**

Author, year published	Overall survival, 1 year	Overall survival, 3 years	Overall survival, 5 years
Verhoeven, 2016 [157]	94.7%	84.6%	-
Oikonomou, 2017 [158]	85.1% (79.1 - 91.1)	75.8% (68.2 - 83.5)	-
Blankensteijn, 2017 [159]	91.4%	86.3%	-
Roy, 2017 [160]	-	-	59.4%
deSouza, 2017 [161]	-	-	92%
Caradu, 2017 [162]	91.4%	82.1% (2 year)	-

It is remarkable that deSouza et.al. report a 5 year overall survival rate of 92% which is conflicting with the one other report in this review which reports that outcome [160]. The study by DeSouza et.al. was comparing matched patients from the US Multicentre Trials of the Zenith Fenestrated Endovascular Graft (William A. Cook Australia PTY. Ltd., Brisbane, Australia) and the Zenith AAA Endovascular Graft (Cook Inc., Bloomington, IN, USA). There is no mention within the study how patients were selected for the fenestrated cohort and there is likely to be significant selection bias for such a study.

Aneurysm related mortality is poorly reported across all studies. Seven patients are reported throughout follow up to have died secondary to aneurysm related causes in six studies that report it.

The following table documents reintervention rates over longer term follow up for studies that analysed their reintervention rate with Kaplan Meier analysis: (See table 7.9)

**Table 7.9 – Long term Outcomes from Included Studies**

<b>Author, year published</b>	<b>Mean or median follow up within study, months (+/- S.D or range)</b>	<b>Freedom from reintervention at 1 yr.</b>	<b>Freedom from reintervention at 3 yr.</b>	<b>Proportion of reinterventions that are Endovascular</b>
<b>Verhoeven, 2016 [157]</b>	21 +/- 15.9	96.1%	90%	73%
<b>Oikonomou, 2017 [158]</b>	33 +/-23	90.6% (85.6 - 95.6)	79.2 (71 - 87.5)	73%
<b>Roy, 2017 [160]</b>	34	-	62.8% (5 years)	82%

The reintervention rate is commonly reported as high after endovascular repair and remains in the region of 10 – 20% during follow up for the studies that report on it. In

addition to the studies in the table above Wang et al. reported an overall 20% reintervention rate over a mean follow up of 20 months. Blankensteijn et.al. reported a 6.7% reintervention rate over 16 months follow up. Importantly the proportion of reinterventions that are purely endovascular also remains high with 75 – 80% approximately being endovascular from the included studies.

The included studies detail that a relatively small but significant proportion of patients still exhibit graft related endoleak during follow up after fEVAR. Verhoeven et al report that 6 patients from an initial cohort of 281 (2.1%) exhibited graft related endoleak at some point during follow up, this study had a mean follow up of 21 months. Oikonomou et. al. reports a rate of 4.2% over a median follow up of 33 months and Roy et al. report graft related endoleak prevalence of 10.4% over 34 months. This highlights the role of continued surveillance and a robust programme to detect and treat complications from endovascular aneurysm repair.

Target vessel patency remains excellent throughout follow up with fenestrated endovascular repair. The range of target vessel patency within the included studies ranges from 95% [159] to 98.9% at 3 years [158]. Roy et al. report a rate of 90.1% target vessel patency at 5 years after initial operation. When details are reported the loss of target vessel is often silent or of little clinical consequence, that being said there is no evidence within the literature to suggest a conservative approach to target vessel threat is a safe strategy. This is particularly true when it comes to the SMA and coeliac axis as the majority of target vessel losses reported in the literature are renal arteries. Low rates of dialysis are seen throughout follow up in the studies that report renal outcomes. There is insufficient evidence within the published literature to suggest whether the endovascular repair has any aetiological role in the development of dialysis in these patients. Rates of renal dysfunction over the longer term are also reported in a heterogenous manner and it is

difficult to draw many conclusions from the literature regarding this, but the range of reported rates is 21 – 27% of patients develop chronic kidney disease over follow up [161, 162]. Overall fEVAR is successful in the majority of patients at preventing aneurysm growth. Little data in individual studies is usually presented on this variable however and not much can be said about it here. For completeness the rates reported in the literature from three studies for aneurysm growth over whole of follow up are 8.3% [159], 9.2% [162], 21% [160].

## **7.5. fEVAR Compared with Alternative Treatment Options**

There have been no randomised controlled trials comparing fEVAR with the variety of alternative treatment options. In fact, there have been no prospective controlled trials of any sort comparing fEVAR with the alternative treatment options. The published studies are either retrospective reviews of patients treated with fEVAR versus a contemporaneous cohort of patients treated with an alternative option or systematic reviews attempting to synthesise results from published studies regarding fEVAR. An assessment published by the National Institute for Health Research Health Technology Assessment (HTA) programme reviewed the published literature widely and failed to find a single comparative study that met their inclusion criteria for assessment of fEVAR versus OR. [166] The studies that are published vary in their methodology and reporting of the outcomes after aneurysm repair making overall synthesis of this part of the literature base difficult.

### **7.5.1. Comparison of fEVAR with Chimney EVAR**

One alternative to fEVAR is the use of the chimney technique. Briefly, this is an endovascular technique of repairing non-standard aneurysms utilising a standard EVAR stent-graft and separate covered stents to maintain blood flow to at least one visceral vessel. Chimney EVAR tends to be used in patients with different anatomical characteristics to that of fEVAR. It is used generally when only one or two visceral vessels

are incorporated into the repair, in those that are unsuitable for fEVAR either because of anatomical constraints or if the presence of symptoms or rupture dictate the need for urgent repair and hence the manufacturing delays inherent in the use of fEVAR prohibit its use. The reports comparing these two techniques are heterogeneous in their indications for use of chimney or fEVAR and in the patients selected for either technique. Banno et al. [167] retrospectively compared fEVAR (80 patients) with chimney EVAR (38 patients) undertaken at their institution and explained that chimney EVAR was reserved for those patients in which it was not possible to place fEVAR and as such those that underwent chimney EVAR had larger aneurysms with longer infrarenal necks, incorporated less visceral vessels and were done in ruptured or symptomatic patients. Bearing these differences in mind, along with other studies, chimney EVAR has shown to have comparable 30-day mortality, complication and reintervention rates versus fEVAR. [148, 167-169] One study however does suggest there may be an increase in stroke rate following chimney EVAR, which seems plausible as unlike fEVAR, chimney EVAR usually utilises the left subclavian artery for access to deploy the side branch stent-grafts. [169] A more recent study by Caradu et.al. compares 90 fEVAR patients with 31 chimney EVAR patients and showed increased 30-day mortality in those patients receiving chimney EVAR. They conclude however that there was no difference in survival at 24 months and the apparent advantages of chimney EVAR should render the two methods as complementary options in the armamentarium of vascular surgeons, to be used in different scenarios. Similar results and sentiments were seen in a systematic review by Li et.al. comparing the two techniques. Rather than being compared as alternatives. As comparative studies the methodology in these published reports is flawed but these studies with short term follow up do seem to suggest relatively equivalent outcomes between fEVAR and chimney EVAR albeit for aneurysms that are anatomically distinct.

### 7.5.2. Comparison of fEVAR with OR

Open repair is still considered by many to be the 'gold standard' for juxta or pararenal aortic aneurysm repair. Of those studies identified within the literature there were two retrospective comparative cohort studies from large international centres performing both OR and fEVAR for non-standard aneurysms, three systematic reviews and two retrospective comparative study utilising a national database. Tsilimparis et al. [91] utilised the American College of Surgeons National Surgical Quality Improvement Programme (ACS-NSQIP) database to collect information on over 1300 (1091 OR, 264 fEVAR) patients who underwent aneurysm repair over a five-year period in the U.S.A. They compared 30-day outcomes and found that patients who underwent fEVAR had a lower; mortality (0.8% vs 5.4%), complication (19.3% vs 42%) and operative reintervention (4.5% vs 10.1%) rate, all of which were found to be statistically significant. The authors compared those with complex aneurysms undergoing OR and those undergoing fEVAR utilising procedure codes from this large national registry. Gupta et. al. performed a similar analysis using the same database but included 535 fEVAR patients and 1207 open repair patients. The 30-day mortality in that study was 2.4% for fEVAR patients compared with 4.7% for open repair patients. However, complex aneurysmal disease, as stated by the authors, could include type IV thoracoabdominal aneurysms which as stated previously represents a distinct anatomical entity to those patients suitable for fEVAR. There was no anatomical information relating to the aneurysms presented within the study and therefore it is difficult to comment on the true ability of this study to compare these two treatment options for similar populations. A single centre study from the U.K. [170] retrospectively compared patients undergoing fEVAR and OR and tried to address the issue highlighted above by excluding any OR patient with a thoracoabdominal aneurysm. Canavati et al. [170] compared 54 patients undergoing OR and 53 patients undergoing fEVAR and found reduced mortality and morbidity rates after fEVAR as well as reduced length of hospital

stay and critical care utilisation after the endovascular approach. The literature gives conflicting reports however on the outcome of fEVAR when compared with OR and one study comparing 42 patients undergoing fEVAR and 147 patients undergoing OR showed that fEVAR was associated with a significantly higher 30-day mortality rate (Odds ratio 5.1), with the crude mortality rates being 9.5% for fEVAR and 2% for OR. [171] This study does have its limitations however and compares patients undergoing fEVAR from an experienced centre in France with those undergoing OR from an experienced centre in the U.S.A. To try and create a relatively homogenous group of patients the authors performed propensity matching with preoperative physiological and anatomical factors. However, by the authors own admission, there were a number of anatomical characteristics that were simply not measured or taken into consideration. It is therefore impossible to truly comment on the complexity of the fEVAR cases included. This may have resulted in fEVAR patients that actually represent a high procedural risk and significant procedural complexity due to their anatomy rather than any physiological score being matched with OR patients of similar physiology. Complex anatomy will have a deleterious effect on the outcome of an operation more readily if that patient were to undergo fEVAR compared with OR. Mainly due to the precise attention to anatomical detail that is required and the small margin for error that exist when deploying fEVAR.

A systematic review of the literature and meta-analysis was conducted and identified 35 case series with data on 2326 patients. [144] Of the total, 1575 patients underwent OR and 751 underwent fEVAR, only two of the included studies reported outcomes for both OR and fEVAR and the remaining were case series of either OR only or fEVAR only. The pooled perioperative mortality rate was 4.1% for both OR and fEVAR suggesting no apparent advantage in terms of short-term mortality. The meta-analysis suggested that more fEVAR patients developed renal insufficiency during follow up, but rates of permanent dialysis were not increased.

### **7.5.3. Comparison of fEVAR with OR and Standard EVAR**

There has been one published study comparing the outcomes of patients undergoing fEVAR, open repair and standard EVAR for aneurysms with 'challenging' infrarenal necks.[121] The study defines a 'challenging' neck as one that is large diameter (>28mm), short (<15mm), angulated (>60°) and/or thrombus lined. The study compared patients treated at two different centres, one in Italy and the other in Sweden. The three groups being compared consisted of 61 OR patients, 74 standard EVAR patients and 52 fEVAR patients. All the patients who underwent OR were treated at the Italian centre and all of those that underwent fEVAR were treated at the Swedish centre. The standard EVAR patients were treated at a mixture of the two centres. Those undergoing endovascular methods were older, had more comorbidities and in general a higher ASA grade. Overall the anatomical characteristics of the aneurysms were similar but those undergoing endovascular repair had shorter and wider infrarenal necks. In this study, there was no statistically significant difference between the three groups in terms of 30-day mortality, aneurysm related mortality during follow up, reintervention rate, renal impairment or need for dialysis during follow up. There was an increase in late aneurysm expansion in the group treated with standard EVAR compared with fEVAR but no other significant findings during the follow up. The mean follow up was almost 20 months. Although this study has limitations especially in terms of the geographic disparity, it appears to show no significant differences between the three treatment options in terms of short-term outcomes.

### **7.6. Learning Curve with fEVAR**

Many publications from early on in the global experience of using fEVAR demonstrate a significant learning effect. As experience has grown and publications from high volume centres continue to report – less is said about learning curve in the recent literature, including those from the above systematic review. This is most probably due to the fact that the centres who continue to publish outcome data have previously demonstrated their

learning curve and are now expert in the deployment of fenestrated technology. Recent papers from 2015 [172] and 2016 [173] document learning curve effects for fEVAR. Starnes et.al. show that over the course of 136 fEVAR procedures performed by one surgeon perioperative mortality or complication rate, procedure length and fluoroscopy time all reduced. This was despite an increase in the complexity of stent-grafts as 53% of cases had 2 or more fenestrations at the beginning of the study compared to 88% towards the end.

Sveinsson et.al. document the experience at two expert centres (in Sweden and France). That study also showed an increase in graft complexity over the 10-year experience. Again, despite increasing complexity those groups found that fluoroscopy time and contrast use decreased as time progressed. They didn't find a difference in clinical outcome measures however such as perioperative mortality, endoleaks or target vessel patency. The French Multicentre study from Haulon et.al. [174] similarly documents a study in which many operators were performing their first fEVAR cases and explains certain results are secondary to the learning curve such as extremes of operative time, fluoroscopy time and contrast use.

Verhoeven et. al. [175] documents the learning curve in his analysis of a single centres outcome over 8 years and cites the fact that half of all target vessel occlusions within that study occurred early on and in non-stented fenestrations and scallops. He goes onto explain it was only after this experience that a policy of stenting all fenestrations was employed. The literature contains many incremental learning steps such as this for endovascular and fenestrated repair, specifically. Verhoeven et.al. also documents a few of the lessons learned through their experience, and technical advances that have made the operation easier for the surgeon:

- The introduction and use of guiding sheaths for deployment of stents within target vessels
- Separate puncture of valve leaves in the sheath to minimise blood loss

- The advent of diameter reducing ties
- The use of a hybrid theatre with fully stocked ancillary equipment
- The reinforcement of scallops/fenestrations to stop infolding of the fabric.

There is no doubt there is a learning curve for fenestrated repair and most authors cite this and reasonably state that complex endovascular techniques should be reserved specialist high volume centres. This intuitively makes sense for these complex procedures, what is unknown however is the learning effect for a single surgeon within an experienced centre and what role the learning effect is experienced by each single operator or by the 'department' as a whole. It is likely that accrued experience of a department and the development of highly tuned processes and team working within each department is maintained despite the introduction of a new surgeon, but this is conjecture.

## 7.7. Discussion

There is an increasing literature base concerning fenestrated endovascular repair available. However, there are no randomised controlled trials or prospectively conducted high quality trials. This makes comparison with other treatment options difficult. The patients selected for fenestrated endovascular aneurysm repair in the majority of studies are, by the authors own admission, unfit for open repair or "high risk" for open repair. This obviously presents a significant selection bias when comparing outcomes of fEVAR with open repair or other methods. One study is notable in its exception to this [157]. It is also interesting to note in that study by Verhoeven et.al. they report a significantly lower perioperative mortality at 0.7% for fEVAR compared with the literature. Of course, this is a high-volume experienced centre with expert operators, but their series is of 281 patients with a mean target vessel ratio per patient of 3.2 vessels per patient. This adds credence to the argument that the true utility of endovascular repair and even fenestrated repair is for the "low risk" patient, not the high risk. Furthermore, reports that compare fEVAR with bEVAR or include these

two treatments together in analyses are comparing and mixing two distinct treatment options. The lack of consistent and robust anatomical criteria for reporting and selection of patients for either treatment is one reason for this problem. Although similar they remain distinct technologies intended for and used (in the majority) for different extents of aneurysms. The lack of clear guidelines on anatomical reporting of aneurysms has exacerbated this problem. The majority of studies that use anatomical definitions for aneurysms that are not considered simply “infrarenal” tend to cite the SVS guidelines on reporting of arterial aneurysms [87]. This document was published in 1991 and does not truly reflect either the information available to clinicians with readily available CT scans that can be reviewed using 3-dimensional software, or the current practice of endovascular repair. Juxtarenal and pararenal aneurysms are terms that are interchangeable in that document and are defined as aneurysms with “no normal aorta below the renal arteries”. This has led many authors to conclude that an acceptable definition of this type of aneurysm is anyone in which a clamp is placed above one renal artery during open repair. This does not consider the fact that a clamp may be placed above the renal arteries for other reasons than aneurysmal extent and that the necessity of a suprarenal clamp does not necessarily mean the anatomy of that particular aneurysm is comparable to one that a physician would undertake standard EVAR, fenestrated EVAR or branched EVAR. Simply put the use of loose anatomical terms such as juxtarenal/pararenal/suprarenal or clamp position does not allow for meaningful comparison and analysis. The recommendation is therefore that these terms should not be used and instead precise and specific anatomic criteria such as neck length, diameter and angulation should be used when reporting on treatments and their outcomes. This will allow comparisons across differing types of repair.

The literature is also significantly heterogenous when it comes to reporting patient characteristics and outcomes such as renal failure. This made any comparison between studies difficult within this analysis.

There has been a progression over the years since the widespread use of fEVAR towards more complex grafts including more target vessels. Several studies have tried to quantify if there is any deleterious effect to the use of more complex grafts more recently. Two studies included in the above analysis (Roy, Oikonomau) analysed the outcomes of less complex graft design (2 or less fenestration) with more complex designs (3 or more fenestration). Neither showed significant differences in outcomes related to graft complexity but the numbers of patients in each group were small. Roy et.al. did show a trend toward higher in hospital mortality in those with more complex designs.

This systematic review and the others in the chapters above deal with each treatment options separately. The following table attempts to synthesise the data for primary outcome measures for all three treatment options from these systematic reviews. Of course, such a comparison is limited due to the multiple potential confounding factors discussed in the above systematic reviews - such as study design, patient population, selection bias but it collates the above presented results together to allow a comparison from the identified literature. First the table presents the outcomes for non-standard aneurysms for the three treatment options (See table 7.10)

**Table 7.10 – Reported Outcomes for NS AAA from systematic Reviews**

<b>Treatment</b>	<b>Primary Technical Success</b>	<b>Perioperative mortality</b>	<b>5-year survival</b>	<b>Aneurysm Related Mortality</b>	<b>Renal Dysfunction</b>
<b>fEVAR<sup>a</sup></b>	95.6%*	2.7%	59.4 – 92%	0.8%	21 – 27%
<b>EVAR</b>	90.7%	3.1%	70 – 85.4%	0 – 6.8%	-
<b>Open Repair</b>	NR	3.2%	64 – 88.6%	1.3%	11.3%

*Table 7.10 – fEVAR – fenestrated endovascular aneurysm repair EVAR – Endovascular Aneurysm Repair. Renal dysfunction is the rate reported over long term follow up. A – The results for fEVAR are collated from the systematic review of 8 studies published since 2015. \* - Adjusted Primary Technical success as reported by Roy et.al.*

The above table collates data for fEVAR from the most recently published data included in the systematic review of the 8 original studies.

Technical success was not reported in any of the open repair studies. For fEVAR two studies report a technical success rate of 79.2% [160] and 85% [159]. Both these studies importantly however comment that this low rate is primarily secondary to intraoperative endoleaks that spontaneously sealed by the time of the first post-operative imaging. When adjusting for this Roy et.al. report a technical success rate of 95.4%. The rate of 95.6% given in the table above uses the adjusted primary technical success rate given by Roy et.al. to calculate.

Five-year survival was not commonly reported across many of the studies for the different treatment options, primarily due to length of follow up time. For EVAR it was only possible from 2 studies [103, 112]. For open repair it was only possible from 4 studies [125-127, 129], for fEVAR – 2 studies [160, 161]. Therefore, only those studies that report 5-year survival using the Kaplan Meier method have been used to create the above table. Since it is not possible to amalgamate the outcomes for 5-year survival from KM method between studies a range is given

It is important to note that the aneurysm related mortality rate for EVAR presented in the table were from studies with a wide range of FU times, so it is given as a range of results across all the studies. The range of mean or median follow up was 12 – 51.6 months in the studies. For open repair AAA related mortality was poorly and inconsistently reported. In those that did mention it there it was often difficult to extract the information. From 4 studies that did mention it – 3 reported 0% and the other reported 5 deaths. The above value is a pooled value of these four studies. Aneurysm related mortality for fEVAR was from 6 of 8 studies, in general it was also poorly reported across the studies. Seven patients out of 845 are reported throughout follow up to have died secondary to aneurysm related over FU ranging 12 – 34 months

As stated in the above systematic reviews rates of renal dysfunction were poorly reported across all studies with differing definitions often for what constituted renal failure. For EVAR it was not possible to provide a value due to insufficient data. For open repair the value was collated from three studies and fEVAR 2 studies.

It is disappointing that a more robust collation of the results cannot be made from the available and analysed literature for the above outcome measures, but primary technical success rates appear to be better for fEVAR when considering the definition of adjusted primary technical success used by Roy et. al. but similar when using the standard definition of technical success (92.3% for fEVAR). Furthermore, the above table highlights that perioperative mortality appears similar across all three treatment options which is surprising given the results of randomised controlled trials comparing open repair and infrarenal EVAR. However as stated there are many confounding factors across these studies and it is difficult to draw firm conclusions from the above presented results.

For completeness the same information is presented for standard aneurysm patients from the literature. (See table 7.11)

**Table 7.11 - Reported Outcomes for SA AAA from RCT**

<b>Treatment</b>	<b>Primary Technical Success</b>	<b>Perioperative mortality</b>	<b>4-year survival</b>	<b>Aneurysm related Mortality</b>	<b>Renal Dysfunction</b>
<b>EVAR</b>	NR	1.4%	84.2%	2.9%	-
<b>Open Repair</b>	NR	4.2%	83%	4.3%	-

*Table 7.11 – EVAR – Endovascular Aneurysm Repair.*

The results from a cochrane review [74] of the four randomised controlled trials comparing open repair with EVAR provide the results for the above table. Primary technical success rates were not reported in that review or in the original studies. In the review there was no

statistically significant difference between the 4-year survival and aneurysm related mortality (also up to 4 years) outcome measures. Renal dysfunction was measured over the longer term in the EVAR 1 trial [64] but reported as change in the eGFR rather than rates of renal dysfunction. The results from that trial showed *“no significant change in the estimated glomerular filtration rate (eGFR) between groups, with a mean (SD) difference from baseline of -1.13 (1.43) and -1.00 (1.43) mL/min/1.73/year in the EVAR and OSR groups, respectively (P = 0.275)”*

## **7.8. Conclusion**

Fenestrated endovascular aneurysm repair has acceptable clinical outcomes both in the short and longer term as outlined above. There is heterogeneity between studies published and especially when concerning comparative studies making valid comparison difficult to draw. The safety, feasibility and efficacy is clear from the published literature. Further work is needed to compare this method of aneurysm repair with alternatives to ascertain its true utility in the context of treating aneurysmal disease. Furthermore, strict guidelines regarding the reporting of anatomical criteria of aneurysm treated should be adhered to within the vascular surgery community when publishing reports of endovascular repair. These guidelines should include details on aneurysm neck morphology, with reference to instructions for use, clamp position and reasons for choosing that position, as well as criteria for comorbidity reporting.

## **8. CHAPTER 8 - A Review of Clinical Outcomes at Royal Liverpool University Hospital after fEVAR**

### **8.1. Introduction**

Fenestrated endovascular aneurysm repair (fEVAR) has become an accepted and widespread technique for the treatment of complex abdominal aortic aneurysms in which the anatomy of the infrarenal neck precludes the placement of a standard endovascular device. It is estimated that to date more than 5000 fenestrated stent-grafts have been implanted worldwide.[176] Following this worldwide experience, many centres have now reported short to mid-term data on clinical outcomes after fEVAR with promising results. Meta-analyses show acceptable mortality, target vessel patency and long-term dialysis rates up to two years and beyond.[92] Whilst these early results support the use of fEVAR as a treatment for complex aneurysms, there remains a paucity of long-term data. This chapter reports the 10-year experience of fEVAR from the Royal Liverpool University Hospital (RLUH), the first hospital in the UK to adopt this technique.

### **8.2. Methods**

This was a retrospective cohort study over 10 years of all patients within a single UK centre (RLUH) who had undergone a primary fEVAR procedure.

#### **8.2.1. Patients and Inclusion Criteria**

Data of all patients who underwent fEVAR were entered into the GLOBALSTAR registry. [85] This is a multi-centre collaborative online project developed within the University of Liverpool and includes the majority of UK fenestrated procedures at the time of writing. GLOBALSTAR is an online registry developed by physicians with data entry performed by physicians that perform the procedure. In the absence of randomised controlled trials, the aims of the GLOBALSTAR project at the outset were to evaluate the technique in terms of

primary and secondary endpoints, establish an archive of all pre-operative and follow up imaging, to aid detection of mechanisms of failure, and to provide an “early warning system” for complications specific to the technique. Retrospective analysis provided patient demographics, aneurysm characteristics, operative details and post-operative surveillance data. It should be noted that anatomical information for each aneurysm is not stored on the database nor are copies of the CT scans. Preoperative imaging was not reviewed as part of this study to ascertain specific anatomical criteria. This was primarily for two reasons; firstly, the review is designed to investigate outcomes after fEVAR as a specific treatment rather than focus on anatomy – to provide a background of the clinical outcomes for fEVAR over a long period of time. Not to compare clinical outcomes for patients with differing anatomy but to detail the mid – long term clinical outcomes for fEVAR. Secondly the use of fEVAR within the Royal Liverpool University Hospital goes back to 2003 and it would have been practically impossible to obtain all CT scans for all those patients to review their anatomy. All consecutive patients who underwent primary fEVAR within the RLUH between Feb 2003 and Feb 2013 were included in this analysis. The data for this study was collated prior to that for the retrospective multicentre study of non-standard aneurysms and data collection for this study stopped in 2014 – four years earlier than the multicentre retrospective study.

Patients who underwent a branched thoracoabdominal endovascular repair, a combined fenestrated and branched endovascular repair and a fenestrated cuff extension device were excluded. The primary endpoints included overall survival, freedom from target vessel loss, graft-related endoleak and secondary intervention. Definitions for success, complications and other events associated with endovascular repair were in accordance with accepted reporting standards.[93, 99] A target vessel is defined according to previous published reports on fEVAR, as “a vessel potentially covered by the stent-graft fabric if not for a deliberate mechanism of preservation, when the stent-graft is deployed as intended.”

### **8.2.2. Follow up Protocol**

There was a standardised post fEVAR surveillance protocol including plain abdominal radiograph (AXR) prior to discharge, one-month duplex ultrasound examination (DUS) and single arterial phase computed tomography angiography scan (CTA), and a six-week clinical review. Six month and then annual AXR, DUS and CTA were undertaken. If complications or potential problems were identified patients were discussed at a multi-disciplinary team (MDT) meeting. Further imaging in the form of dual or triple phase CTA or contrast-enhanced ultrasound (CEUS) were performed if deemed appropriate and secondary intervention was undertaken if clinically indicated.

### **8.2.3. Statistics**

Continuous data are presented as a median with the range in parentheses. Overall survival, freedom from target vessel loss, graft-related endoleak and secondary intervention were all subject to Kaplan-Meier analysis. Median follow up length was determined using the reverse Kaplan-Meier technique. SPSS version 20.0 (SPSS Inc, Chicago, Ill; [www.spss.com](http://www.spss.com)) was used for all statistical analyses. If the patient was known to be alive and still on the surveillance programme their last point of follow up was taken as the point of data collection. If the patient was followed up elsewhere and hence not in the local programme, then their last point of imaging was taken as the last follow up time point.

### 8.3. Results

During the 10-year study period 115 patients underwent a branched and/or fenestrated procedure of which 107 underwent primary fEVAR. Eighty-nine per cent were male and the median age at operation was 75 years (53 – 88). Median pre-operative aneurysm size was 64mm (55-92) and median post-operative follow up was 51 months (1 – 124). Patient comorbidities and American Society of Anesthesiologists (ASA) grading are detailed in table 8.1 (See table 8.1). The median pre-operative creatinine level was 101  $\mu\text{mol/L}$  (51 - 762), and the median BMI was 28 (19-41). There was information pertaining to pulmonary function testing in 87% of patients with a median forced expiratory volume in one second of 2.08 L (0.82 – 4.87). Pre-operative left ventricular ejection fraction was not recorded in 48 patients (45%)

*Table 8.1 Patient Characteristics*

Comorbidity	Percentage of patients
Diabetes	14
Ischaemic heart disease	50
Congestive heart failure	8
Hypertension	58
Chronic kidney disease	20
Previous vascular disease	14
ASA Grade	
I	2
II	22
III	70
IV	4
Data missing	2

### 8.3.1. Operative Data

All devices in the 107 patients were introduced successfully with no target vessel loss upon completion of the procedure. There were, however, 15 patients with a graft-related endoleak (type I or III) on completion angiography, giving a primary technical success of 86% (92 patients). Thirteen of these fifteen endoleaks identified had resolved without intervention at the one-month surveillance imaging.

There were 31 intraoperative adjunctive manoeuvres used in 28 patients. (See table 8.2)

*Table 8.2 Intraoperative Adjunctive Manoeuvres*

<b>Adjunctive manoeuvre</b>	<b>n</b>
Extra renal stent placed	4
GTN for renal artery spasm	4
Renal stent reinflated to correct endoleak	3
Renal artery predilated (Pre-existing stenosis)	1
Iliac angioplasty	5
Adjunctive iliac limb stent because of kinking	4
Femoro-femoral crossover	2
Bilateral common femoral artery endarterectomy	1
Iliac conduit	1
Coda balloon to proximal main body to rectify endoleak	2
'Crossover technique' as unable to cannulate contralateral stump	1

The median operation time was five hours (3 hrs. 15mins – 11 hrs.), with data available in 85% of patients.

### 8.3.2. Stent-graft Configuration

The most common stent-graft and target vessel configuration was a scallop for the superior mesenteric artery (SMA) and a small fenestration for each of the renal arteries (50%). (See table 8.3)

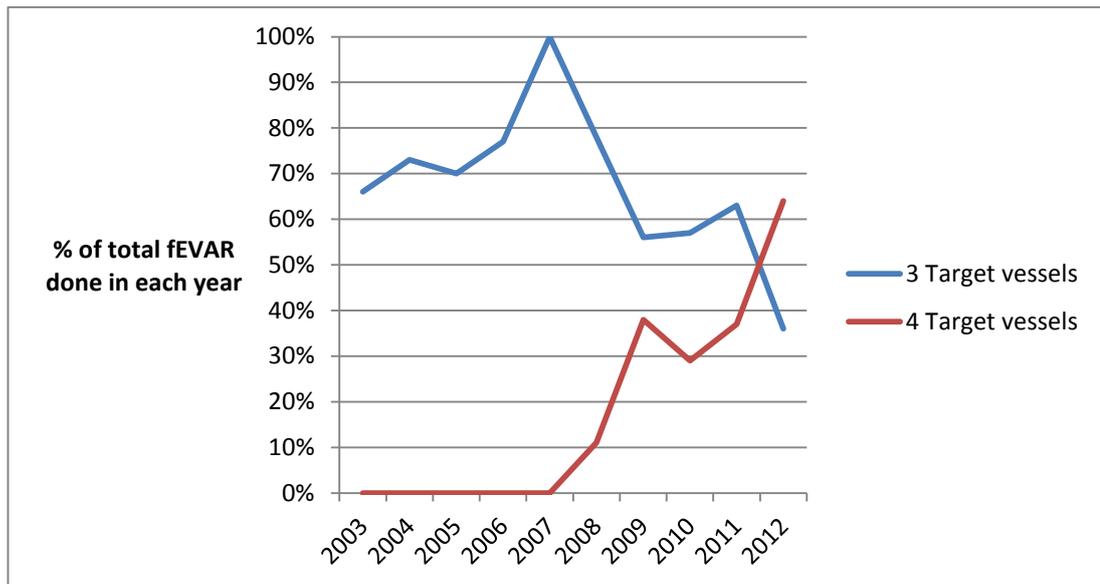
**Table 8.3 Stent-Graft Configuration**

<b>Number of Target vessels</b>	<b>Configuration</b>	<b>Number of patients</b>
<b>4</b>	Fen CA/SMA/LRA/RRA	5
	Sc CA, Fen SMA/LRA/RRA	21
<b>3</b>	Fen CA/SMA/LRA	1
	Sc CA, Fen SMA/LRA	2
	Sc CA, Fen SMA/RRA	1
	Fen SMA/LRA/RRA	9
	Sc SMA, Fen RRA/LRA	53
	Sc SMA, Fen LRA, Sc RRA	1
<b>2</b>	Fen CA/SMA	1 <sup>a</sup>
	Fen SMA/RRA	1
	Sc SMA, Fen RRA	1
	Fen RRA/LRA	1
	Fen RRA, Sc LRA	2
<b>1</b>	Sc RRA or LRA	8

**Table 8.3 - a - Patient with end-stage renal failure on dialysis. Fen = Fenestration, Sc=Scallop, CA = Coeliac axis, SMA = Superior mesenteric artery, LRA = Left renal artery, RRA = Right renal artery.**

Over the ten-year period studied there were an increasing proportion of stent-grafts incorporating four target vessels in the repair. (See figure 8.1)

**Figure 8.1 Proportion of 3 and 4 Target Vessel Stent-Grafts Implanted Over Time**



### 8.3.3. Target Vessels

There were 325 target vessels in 107 patients. Of these, 90 were preserved with a scallop and 235 with a fenestration (72%). It was routine practice to stent all fenestrations however this was not possible in four instances. One was due to an inability to cannulate the celiac axis, and in another a large fenestration with struts crossing the opening was manufactured and therefore the target vessel was not stented. There was no reason recorded for the lack of stenting in the other two. Furthermore, eight renal arteries that were protected with a scallop were stented in this series. In total 239 target vessels were stented with details on type of stent available for 225 (94%). Bare metal stents were used in 70 target vessels (Palmaz Genesis, Cordis Corp.= 53; AVE, Medtronic Inc. = 15; Racer RX, Medtronic Inc. = 1; Unspecified in 1). Covered stents were used in 155 target vessels (Advanta, Atrium Medical = 141; Jotec stent-graft, Abbott vascular = 14).

All target vessels were patent at completion of the procedure. However, in four patients there was a compromise noted to a single renal artery. In one right renal artery the flow was noted to be reduced with no additional procedure undertaken. The patient suffered mild renal impairment without clinical sequelae. In another, occlusion of an intra-renal

artery was noted, most likely secondary to thromboembolisation. The patient suffered a degree of renal impairment not requiring dialysis. Another renal artery was dissected at the origin due to difficult cannulation however, the patient suffered no complications or change in renal function. In the last patient, there was loss of perfusion to the lower pole of one kidney secondary to a dissection beyond the renal stent. No additional procedure was undertaken, and the patient died three days later secondary to extensive systemic cholesterol embolisation and gut ischaemia.

#### **8.3.4. Perioperative Mortality and Complications**

Three patients (2.8%) died within 30 days of the original procedure and one further patient during their primary admission giving a total in hospital mortality of 3.7%. The cause of death for each patient is outlined below:

1. The patient suffered systemic cholesterol embolisation and died from gut ischaemia three days after the operation.
2. The patient died of myocardial infarction four days after operation.
3. The primary procedure was prolonged, lasting ten hours and the patient developed bilateral acute-on-chronic lower limb ischaemia. Bilateral fasciotomies and femoro-femoral crossover were performed but the patient died from multi-organ failure on day nine.
4. The patient died after 47 days having suffered a myocardial infarction and developing cardiac failure.

In the post-operative period, 32 patients (30%) suffered 41 complications, (See table 8.4) of whom eight required a secondary intervention prior to discharge.

**Table 8.4 Post-Operative Complications**

Type of Complication	Complication	n
<b><u>Infection</u></b>	Chest infection	8
	Urinary tract infection	4
<b><u>Cardiac</u></b>	Atrial fibrillation	5
	Myocardial infarction	4
	Pulmonary oedema	2
<b><u>Groin issues</u></b>	Haematoma	2
	Pseudoaneurysm	1
	Post op bleeding	1
<b><u>Ischaemic</u></b>	Mesenteric ischaemia	2
	Lower limb neuropathy	1
	Lower limb ischaemia	1
<b><u>Gastrointestinal</u></b>	Peritonitis	1
	Upper GI bleed	1
<b><u>Other</u></b>	CVA/TIA	2
	Cholesterol embolism	2
	Sepsis	1
	Confusion	1
	Epistaxis	1
	HIT	1

Table 8.4 - GI = Gastrointestinal, CVA = Cerebrovascular accident, TIA = Transient ischaemic attack, HIT = Heparin induced thrombocytopenia.

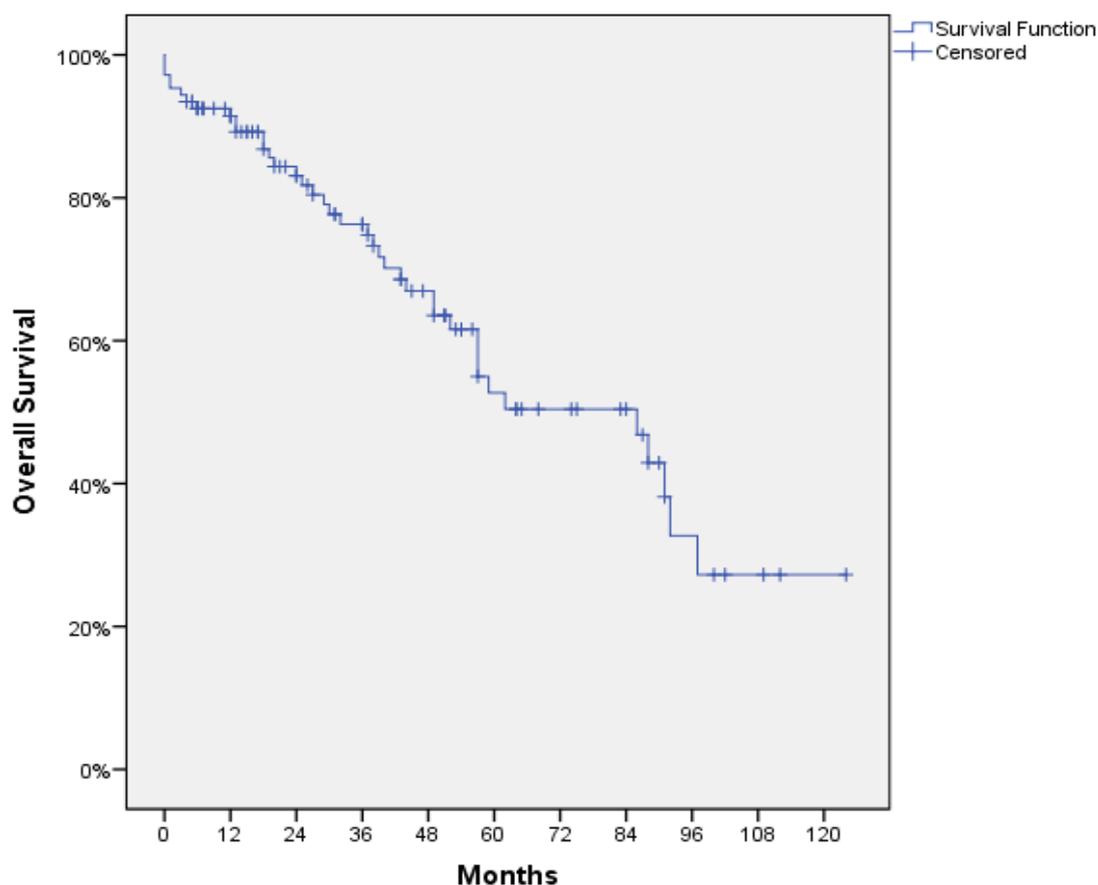
### 8.3.5. Renal Function

Post operatively 30 patients (28%) suffered a greater than 25% increase in their baseline serum creatinine level. Of these, six patients had an abnormal creatinine preoperatively (>130 µmol/L). Two patients with pre-existing renal dysfunction required temporary dialysis while an inpatient. No patient went on to require permanent dialysis after discharge. Data on contrast volume was unavailable for analysis.

### 8.3.6. Overall Survival

At 1, 3- and 5-years' overall survival was 91%, 76% and 53% respectively. Four patients died during their primary hospital admission and 36 died during follow up. None are known to be aneurysm related (See figure 8.2)

*Figure 6.2 K-M Estimated Overall Survival*

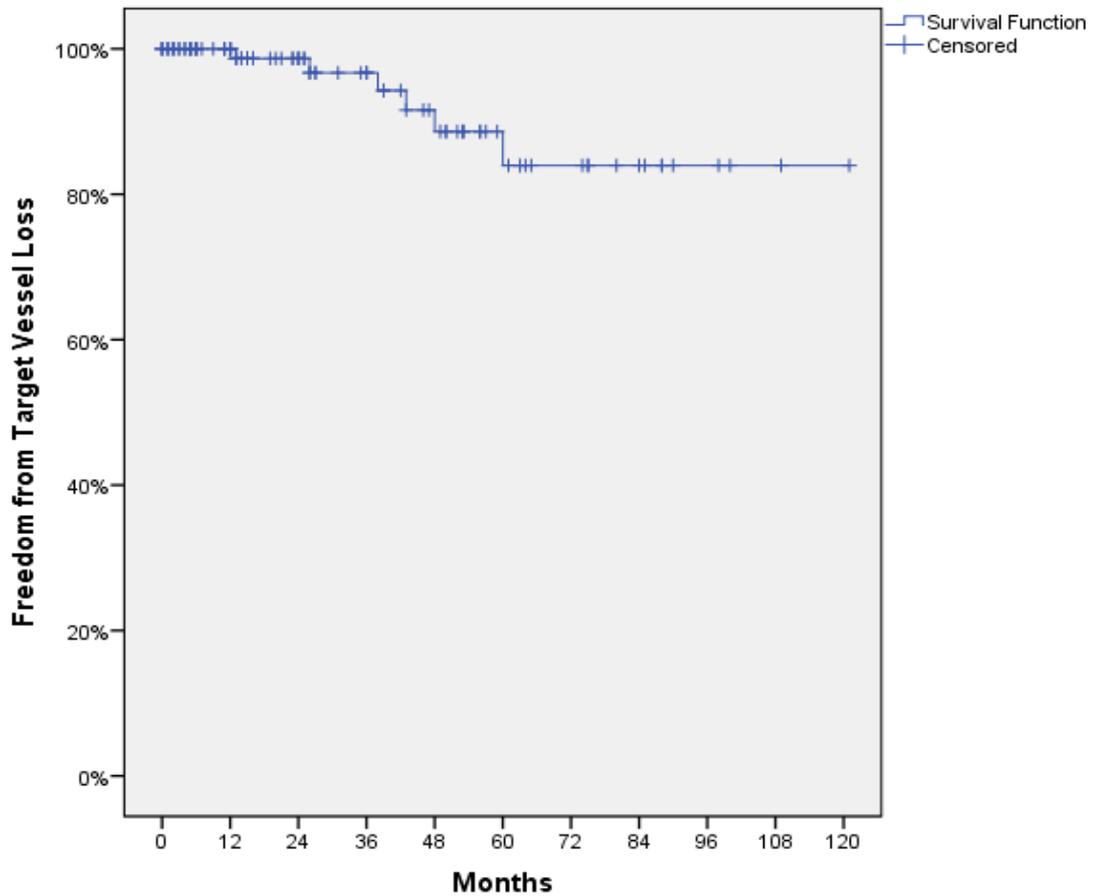


Months	12	24	36	48	60	72	84	96	108	120
Cumulative events	8	15	21	27	34	35	35	39	40	40
Number at risk	95	66	54	39	23	18	15	6	3	1

### 8.3.7. Target vessels

Freedom from target vessel (TV) loss was 100%, 97% and 89% at 1, 3 and 5 years respectively. (See figure 8.3)

*Figure 8.3 K-M Estimated Freedom from Target Vessel Loss*



Months	12	24	36	48	60	72	84	96	108	120
Cumulative events	0	1	2	4	5	6	6	6	6	6
Number at risk	80	55	43	31	19	13	9	4	2	1

During follow up six target vessels occluded. All occurred after 12 months from the initial operation at a median of 20 months (13 – 48). In five patients, the target vessel was a renal artery and one was an SMA, all were stented through a small fenestration. Four of these target vessels received a Palmaz genesis stent and two had a Jotec stent-graft. The mode of failure was recorded in four patients: angulation between TV stent and main stent-graft body in three; and shuttering of a misplaced SMA stent in one. In three cases a problem was identified on surveillance imaging with the target vessel in question prior to the date of

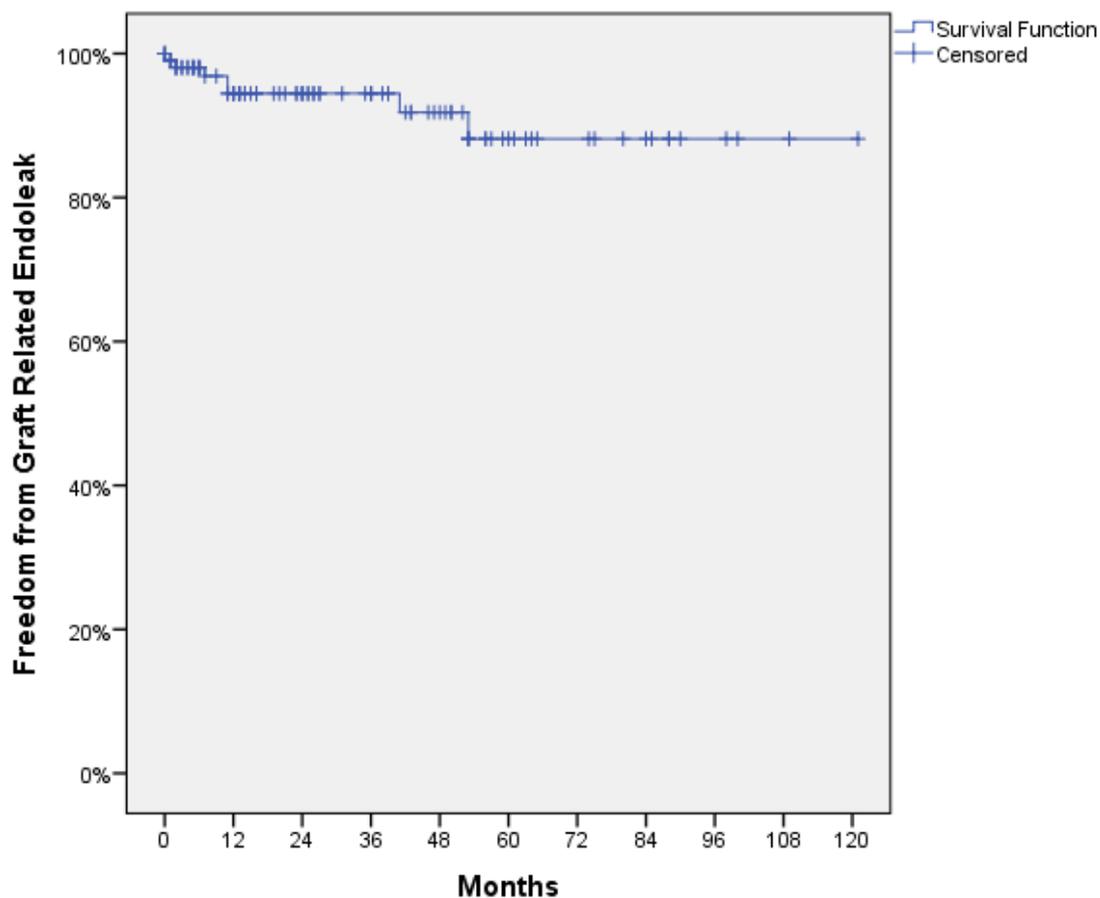
occlusion. In the other three cases, there were no such heralding phenomena. No patient required permanent dialysis or further intervention following their target vessel occlusion.

During post-operative surveillance, the patency of 51 target vessels (16%) in 34 patients was threatened. The mode of threat was as follows: in-stent stenosis (13 TV), native vessel stenosis (8 TV), angulation (10 TV), stent fracture (7 TV), shuttering (6 TV), stent dislocation (6 TV), and vessel dissection (1 TV). Secondary intervention for target vessel threat was carried out in nine patients: three stenoses were stented, one was stented then later underwent a surgical bypass, two target vessels with stent-fracture were re-stented, one shuttering was stented and two patients underwent a diagnostic angiogram revealing no demonstrable pressure gradient across the target vessel of interest therefore no further intervention was carried out. Secondary intervention for target vessel threat occurred at a median of 8 months (<1 – 42) post operatively.

### 8.3.8. Endoleak

Freedom from graft related endoleak was 98%, 96% and 89% at 1, 3 and 5 years respectively. (See figure 8.4)

*Figure 8.4 K-M Estimated Freedom from Graft Related Endoleak*



Months	12	24	36	48	60	72	84	96	108	120
Cumulative events	4	4	4	5	6	6	6	6	6	6
Number at risk	77	54	43	30	17	12	9	4	2	1

There were six graft related endoleaks found during the post-operative surveillance period. All were para-ostial endoleaks related to the connection between renal target vessel stents and the main stent-graft body. Three patients had a secondary intervention that abolished their endoleak, confirmed on subsequent CTA. One patient had a secondary intervention, which abolished the endoleak on completion of the procedure but recurred on surveillance

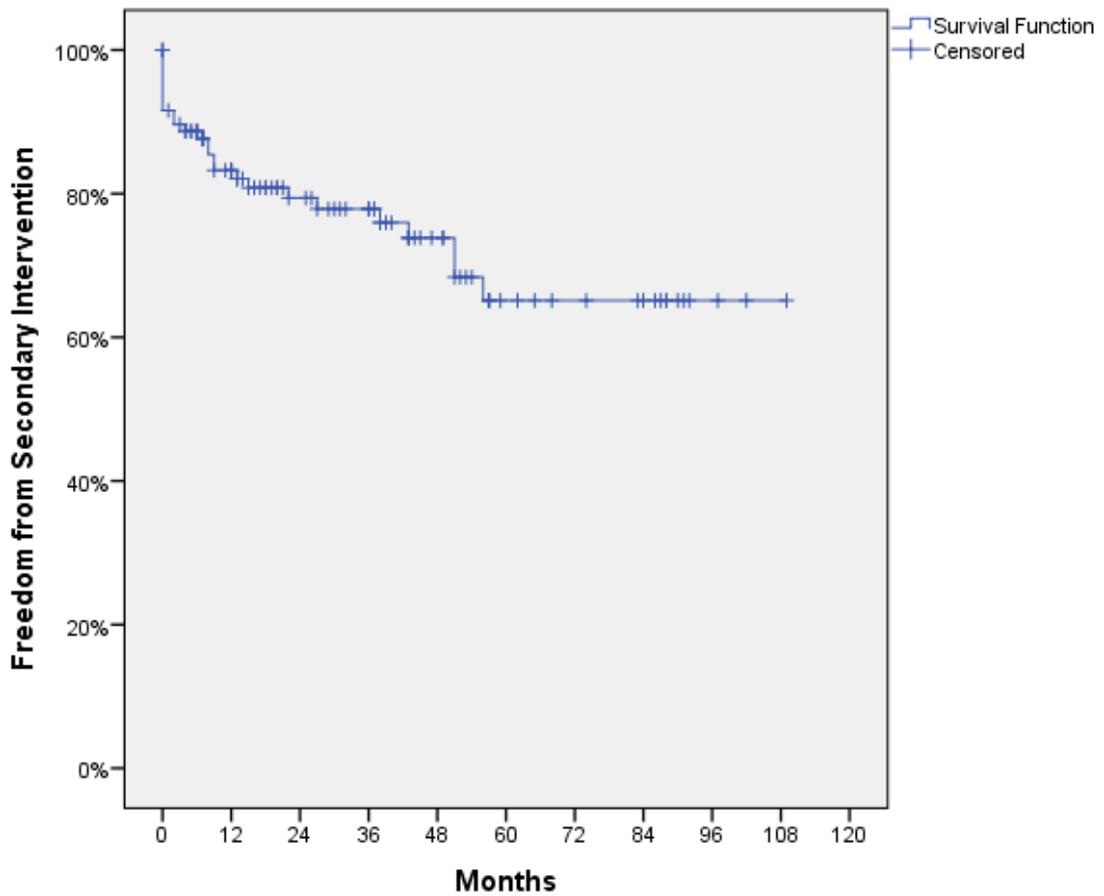
imaging. One patient remains under surveillance with a para-ostial endoleak and one patient was lost to follow up.

During the follow up period, 39 patients (36%) had a type II endoleak. Two patients underwent a secondary procedure to treat their type II endoleak; both patients had an increase in aneurysm size of  $\geq 5$ mm. One patient had a successful IMA embolization at 15 months with subsequent regression of aneurysm size and no further endoleak on surveillance. The other patient had embolisation of a lumbar artery feeding a type II endoleak at 7 years. No further type II endoleak was seen but the patient remains on the surveillance programme with an increasing aneurysm and no endoleak identified on either CTA or CEUS.

#### **8.3.9. Secondary Intervention**

Freedom from secondary intervention was 83%, 78% and 65% at 1, 3 and 5 years respectively. (See Figure 8.5)

*Figure 8.5 K-M Estimated Freedom from Secondary Intervention*



Months	12	24	36	48	60	72	84	96	108	120
Cumulative events	17	20	21	23	26	26	26	26	26	26
Number at risk	74	54	46	29	16	13	11	3	1	0

Twenty-six patients underwent 34 secondary interventions during follow up. The most common indications for a secondary intervention were endoleak, pending loss of seal, and threatened target vessel patency. Five patients had two secondary interventions and one patient had four during the follow up period. The majority of all secondary interventions were endovascular procedures (82%). The secondary interventions are detailed below. (See table 8.5)

*Table 8.5 All Secondary Interventions*

<b>Time after operation</b>	<b>Intervention</b>	<b>Reason for intervention</b>
<b>Within 30 days</b>	Left hemicolectomy	<i>Mesenteric fibromatosis leading to perforation</i>
<b>Within 30 days</b>	Groin exploration	<i>Bleeding from groin</i>
<b>Within 30 days</b>	Groin exploration	<i>Bleeding from groin</i>
<b>Within 30 days</b>	Fem-fem crossover and fasciotomies	<i>Lower limb ischaemia</i>
<b>Within 30 days</b>	Bilateral renal stent PTA	<i>Proximal endoleak</i>
<b>Within 30 days</b>	Renal stent PTA	<i>Endoleak around renal stent</i>
<b>Within 30 days</b>	Renal stent PTA	<i>Stenosis of stent</i>
<b>Within 30 days</b>	Wallstent	<i>Kinked limb</i>
<b>1 month</b>	SMA PTA	<i>Mesenteric ischaemia</i>
<b>3 months</b>	EIA stent	<i>Dissection of EIA</i>
<b>3 months</b>	Renal artery stent	<i>Endoleak around renal stent</i>
<b>4 months</b>	IIA embolisation and extension into EIA	<i>Minimal seal</i>
<b>4 months</b>	Groin exploration	<i>Bleeding from groin</i>
<b>7 months</b>	SMA stent	<i>Stenosis in native vessel</i>
<b>8 months</b>	Diagnostic angiogram	<i>? Stenosis right renal stent (No stenosis found)</i>
<b>8 months</b>	Renal artery stent	<i>Shuttering of renal artery</i>
<b>8 months</b>	EIA to SMA bypass	<i>Mesenteric ischaemia</i>
<b>10 months</b>	Diagnostic angiogram	<i>Increased velocity in SMA (No pressure gradient on angiography)</i>
<b>12 months</b>	Renal stent PTA	<i>Endoleak around renal stent</i>
<b>13 months</b>	Further SMA stent	<i>Fractured SMA stent</i>
<b>14 months</b>	Renal stent PTA	<i>Endoleak around renal stent</i>
<b>15 months</b>	IMA embolisation	<i>Type II endoleak and enlarging aneurysm</i>
<b>22 months</b>	Bilateral limb extension	<i>Poor engagement bilaterally</i>
<b>2 years</b>	Further SMA stent	<i>Fractured SMA stent</i>

<b>3 years</b>	Diagnostic angiogram	<i>Angulated and fractured renal stent (No intervention as renal artery occluded)</i>
<b>3 years</b>	SMA stent	<i>Stenosed SMA</i>
<b>4 years</b>	Bridging stent	<i>Modular distraction</i>
<b>4 years</b>	Wallstent	<i>Kinked limb</i>
<b>4 years</b>	Bilateral Wallstents	<i>Bilateral Kinked limbs</i>
<b>5 years</b>	Bridging stent	<i>Modular distraction</i>
<b>6 years</b>	Wallstent	<i>Stenosis within limb</i>
<b>7 years</b>	Relining with bifurcated stent-graft	<i>Modular distraction</i>
<b>7 years</b>	Lumbar artery embolization	<i>Type II endoleak and enlarging aneurysm</i>
<b>8 years</b>	Diagnostic angiogram	<i>Enlarging aneurysm</i>

Table 8.5 - PTA = percutaneous transluminal angioplasty, SMA = Superior mesenteric artery, EIA = External iliac artery, IIA = Internal iliac artery, IMA = Inferior mesenteric artery

### 8.3.10. Aneurysm growth

With regards to aneurysm growth during follow up, when comparing the pre-operative planning CTA and the most recent CTA; 57 patients (57%) had aneurysm shrinkage of  $\geq$  5mm, 31 patients (31%) had between 5mm of aneurysm shrinkage and 5mm of aneurysm growth, and 12 patients (12%) had aneurysm growth of  $\geq$  5mm. Data were not available for 7 patients.

## 8.4. Discussion

Fenestrated endovascular aneurysm repair is an effective and safe method for treating aneurysms not suitable for standard endovascular repair in the short to medium term. In this cohort, there was an in-hospital mortality of 3.7%. This is in-line with other contemporary single and multi-centre studies. [82, 84] Meta-analyses have reported a pooled mortality rate of 2% [149] and 2.5% [92] within 30-days. Again, these results are equivalent to this analysis where the 30-day mortality was 2.8%. For comparison, systematic reviews of open repair of juxta or pararenal aneurysms show that the mortality rate and dialysis rates are comparable with endovascular repair in these aneurysms.[177, 178]

The main limitations in this analysis were its retrospective nature and the fact that 10 patients did not have their long-term post-operative surveillance at RLUH. Seven of these patients had their initial fEVAR procedure prior to 2008 and three had it in 2009. After this point there was a conscious decision to continue long term post-operative surveillance within the unit conducting the initial fEVAR to ensure that the rigorous follow-up protocol was adhered to in all patients. Even though 10 patients were followed up elsewhere long-term surveillance data were fed back to the initial operating centre thereby providing valuable data for analysis. For those 10 patients, the median length of follow up data that were available was 23 months (6 – 75).

All stent-grafts were implanted successfully in this series; however, there was a primary technical success rate of 86%. This loss of primary technical success was due entirely to graft-related endoleak noted at completion angiogram in 15 patients. Twelve patients had resolution of their endoleaks, without intervention, by the first post-operative CTA and remained endoleak-free for the remainder of their surveillance. The details of the other three patients are detailed below:

- One patient, with a proximal type I endoleak at the end of the procedure, that had resolved by the time of the first post-operative CTA, developed a para-ostial endoleak at the left renal stent 53 months later. This was due to caudal migration of the stent graft ultimately leading to dislocation of the left renal stent. The endoleak was not communicating with the aneurysm and the patient remained on the follow up surveillance programme.
- A further patient who had a type III endoleak between the target vessel stent and main body on completion angiogram had two secondary procedures; the first was an angioplasty to 're-lock' the left renal stent to the fenestration prior to discharge and a second renal stent three months later which abolished the endoleak. However, 15 months after the primary procedure the endoleak was present on CEUS with a stable aneurysm size, this patient remained on the follow up surveillance programme.
- The remaining patient died before discharge of multi-organ failure preceded by an acute myocardial infarction.

There has been apprehension relating to the possibility of type I endoleaks after fEVAR, as the presence of target vessel stents within the proximal seal zone makes it undesirable to use balloon moulding of this area to try and abolish the endoleak, an effective technique in standard EVAR. Two of the nine patients noted to have a proximal type I endoleak on completion angiogram underwent balloon moulding of the proximal seal zone, both unsuccessful at abolishing the endoleak. Neither patient required secondary intervention for their target vessels nor suffered target vessel occlusion. Due to the risk of disrupting the target vessels, it was not routine practice to undergo adjunctive balloon moulding of the proximal sealing zone at the time of the operation. It is important to note that in all nine of these patients the endoleak was not present on the first post-operative CTA at one month and was never seen again during their follow-up. This highlights that fears of early proximal

endoleaks in fEVAR leading to clinical failure may be exaggerated. It has now become standard practice at RLUH to manage conservatively small proximal endoleaks noted at completion angiogram.

With this technology in the second decade of its application, it is now possible to analyse the longer-term outcomes to determine the true utility of this technique. One area of concern since the introduction of this technology is the potential for target vessel loss during the longer term with potentially catastrophic clinical consequences. Freedom from target vessel loss was 89% at 5 years in this series. The attrition rate of target vessels is therefore surprisingly low even in the long term, and none of the six target vessels that occluded resulted in serious clinical consequences for any patient. This is within the context of a robust surveillance programme that identifies and can act upon threats to target vessel patency. These results are in line with another long-term study with median follow up of 67 months [84] confirming that target vessel loss does not appear to be a significant problem with fenestrated technology.

Late re-intervention remains an important disadvantage of endovascular techniques and fEVAR is no exception. However, in our series secondary interventions performed after discharge were, in the main, endovascular procedures (82%). The frequency of re-intervention confirms the necessity of continued robust surveillance.

Since the UK EVAR trials have shown an advantage to endovascular repair in terms of mortality in the short term [64] it has been assumed this advantage is maintained when dealing with juxta-renal aneurysms and fEVAR. With the lack of a randomised controlled trial there has continued to be a desire to compare fEVAR with open surgical repair using the best available evidence to determine the true utility of the endovascular technique in this setting. However, there have been few studies that compare the two strategies directly, which make it difficult to ascertain the true advantage of fEVAR. Furthermore, as

standard stent-graft technology and techniques have improved over the past 10 years the scope and range of aneurysms that are now suitable for standard endovascular repair is significantly larger than it was 10 years ago. This means that reports on open repair prior to this time for 'juxtarenal' aneurysms may include patients in whom their aneurysm would now be suitable for standard repair. This, again, makes it difficult to draw comparisons between historic reports for open repair and contemporary reports for fEVAR. It may therefore now be appropriate to move away from defining infrarenal aneurysms anatomically and towards an endovascular based delineation – 'standard' aneurysms; for those aneurysms that are suitable for standard EVAR and 'non-standard' aneurysms for those that are not. This would focus further study in this area to compare anatomically equivalent aneurysms undergoing the two treatment options. In a recent analysis of patients, from the RLUH, who underwent open repair for 'non-standard' aneurysms between 2006 and 2010 the perioperative mortality rate was 9.2% with an absolute risk reduction for fEVAR of 5.5% when compared with open repair. [170]Therefore, it was correct to assume the preservation of the short-term advantage seen in standard EVAR, in this centre at least. Along with this analysis showing the durability of fEVAR in the long term these results show fEVAR to be a feasible, safe and durable technique for repairing 'non-standard' abdominal aortic aneurysms.

## **8.5. Conclusion**

This chapter details the experience from the first centre in the UK to adopt fEVAR. It highlights the excellent technical success, low perioperative mortality and high clinical success rates seen in the short and mid-term. Furthermore, it shows that initial successes as regards freedom from graft-related endoleak and target vessel patency are maintained in the long term. A robust surveillance programme along with significant experience of fenestrated endovascular repair and the various modes of failure is necessary in order to provide fEVAR as an option that is durable in the long-term.



UNIVERSITY OF  
LIVERPOOL

A Comparison of Fenestrated  
Endovascular Aneurysm Repair (fEVAR)  
with Alternative Treatment Strategies  
(Volume 2)

*Thesis submitted in accordance with the requirements of the*

*University of Liverpool for the degree of*

*Doctor of Medicine*

By

**Alistair Mackenzie Millen**

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## **9. CHAPTER 9 – A Multicentre Retrospective Concurrent Cohort Study of Clinical Outcomes following Non-Standard Aneurysm Repair**

### **9.1. Introduction**

The treatment options for patients with non-standard aneurysms is varied and multiple, especially as technology continues to advance. However, the three most commonly used methods to repair a non-standard aneurysm are still open surgical repair, standard EVAR and fenestrated EVAR.

For standard infrarenal aneurysms it is relatively well understood from the gathered evidence that EVAR confers a short-term benefit over open repair in terms of perioperative mortality, but this advantage appears to equalise over time. The compromise for this early advantage is an increased risk of late failure and need for reintervention in the future. When EVAR is used outside its IFU it exhibits inferior clinical outcomes when compared to EVAR within IFU such as increased type 1 endoleaks, reintervention rates and there is a suggestion that mortality may be increased over the longer term. It is not clear however the exact magnitude of these deleterious effects and whether when compared to alternative treatment options for non-standard aneurysms they will remain inferior clinical outcomes. Open surgical repair for non-standard aneurysms has been shown to be possible with low mortality rates from the literature. However, this finding is certainly not consistent across all studies. In addition to this the heterogeneity within the published literature to date and the use of loose anatomical terms such as juxtarenal aneurysm makes the outcomes for specific cohorts of patients with defined anatomical characteristics uncertain.

Fenestrated EVAR has been shown to be safe and effective in the short and mid-term but more recently with increasing stent graft complexity a concern has arisen that the limits of this technology are being pushed too far and outcomes are worsening for patients with more complex anatomy and treatments.

It seems intuitive and to some extent is backed up from the published literature that when endovascular repair is tested to the boundaries of anatomy that it is designed to treat outcomes tend to worsen and this seems to be true for standard EVAR and may well be true for fenestrated EVAR. With continuing enthusiasm for endovascular repair and technological advancements both standard EVAR and fenestrated EVAR are being pushed to the limits of anatomy that they can safely treat, i.e. they are both moving proximally. Since no randomised controlled trial or prospective trial has been conducted to assess the outcomes of non-standard aneurysms all the available evidence within the published literature is from cohorts of patients being treated more aggressively both with EVAR and fEVAR as the years proceed. Due to this there is a gap in the understanding of whether an EVAR placed outside of IFU confers better or worse clinical outcomes than a fEVAR placed well within its IFU with the minimum number of target vessels possible. This supposition provides the rationale for this research. In essence – for those patients that are out with the treatment of standard EVAR or infrarenal open repair (which is usually because of an unsuitable infrarenal neck – making them juxtarenal aneurysms) what are the advantages and disadvantages of the three most common treatment strategies? To investigate this question the following hypothesis and study were designed.

## 9.2. Hypothesis:

Fenestrated Endovascular Aneurysm Repair (fEVAR) has superior clinical outcomes as a treatment strategy for non-standard AAAs that are unruptured in whom aneurysm repair is deemed to be more beneficial than conservative management.

The term “superior clinical outcomes” is in relation to all cause and aneurysm related mortality at all time points both perioperatively and throughout follow up. For the purposes of the hypothesis these primary outcome measures carry an equal weighting towards the definition of “superior clinical outcomes” to reflect the need for aneurysm repair to prevent death both in the short and longer term. Aneurysm related, and all-cause mortality are equally weighted to reflect the desire for any given treatment option to be superior to its alternatives both in improving survival from the condition and in providing an overall benefit to any given patient. This is because, for an individual patient, mortality has the same devastating effect whether it is caused by the aneurysm or not. It remains important however to demonstrate (if possible) that a treatment reducing mortality from the condition it is treating regardless of all-cause mortality which inevitably is influenced by unrelated confounding factors. Other clinical outcome measures that will be considered to contribute to whether fEVAR is “superior” will be technical success and clinical success as defined by agreed reporting standards.[93] These outcome measures will inform the decision of whether the hypothesis is satisfied or not and to reflect the importance of continued clinical efficacy throughout follow up clinical success will have a greater weighting to technical success in making this decision but less of a weighting than the outcome measures related to mortality. This reflects the fact that each of these represents the ability of the method of repair to exclude the aneurysm from the circulation without demonstrable major consequences that potentially affect the patient’s quality of life in a measurable and quantifiable way.

## 9.3. Methods

### 9.3.1. Definition of non-standard aneurysm

The definition used within this study for non-standard aneurysm has already been set out in the chapter on study design but is reiterated here. For the purpose of this study it was important to develop a term that specifically defines the anatomy of interest and the patient population being studied. The patient population of interest was patients that were not suitable for standard endovascular repair according to anatomical criteria pertaining to the infrarenal neck. The term non-standard aneurysm/non-standard anatomy was developed to describe any anatomy of the infrarenal neck that fell out with standard EVAR indications for use.

In this study the definition of non-standard aneurysm therefore applied to any aneurysm that exhibited any one of the following criteria:

- 1) A neck length of <10mm
- 2) An alpha angle of > 60 degrees
- 3) A beta angle of >75 degrees.
- 4) Neck diameter >32mm (but  $\leq$  36mm)

Moreover, if the neck length was 10 – 15mm AND one of the following apply then it is non-standard (in keeping with the IFU for the endurant stent graft:

- 5) Alpha angle >45 degrees
- 6) Beta angle >60 degrees.

These anatomical characteristics define non-standard anatomy but there is an important caveat within the definition of non-standard anatomy that was used in this study: If an aneurysm was treated with a specific endovascular device and the anatomy was in breach of the IFU for that device in any way then it was deemed non-standard. In order to exclude

patients that possessed a thoracoabdominal aneurysm and one that would traditionally necessitate placement of a branched endovascular stent-graft if treated endovascularly it was deemed that if an aneurysm possessed a neck diameter of >36mm immediately below the level of the renal arteries then this would exclude it from the definition of a non-standard aneurysm and instead it would be defined as a thoracoabdominal aneurysm.

In summary the definition of a non-standard aneurysm is those that are out with the IFU for standard EVAR but within that for fenestrated EVAR.

### **9.3.2. Geographical and Temporal Location:**

To test the hypothesis a retrospective concurrent cohort study was carried out assessing the clinical outcomes of three categories of patients: those treated by traditional open operation, fEVAR, and a standard EVAR performed outside of IFU. Analysis of all patients who underwent aneurysm repair for a 'non-standard aneurysm' in the Cheshire and Merseyside region in the 24-month period 1<sup>st</sup> April 2006 – 31<sup>st</sup> March 2008 were to form the basis of data for this study. There were seven centres within the Cheshire and Merseyside region that performed at least one of the three treatment methods during the study period. These included; the Royal Liverpool University Hospital, Aintree University Hospital, Southport Hospital, Warrington Hospital, Arrowe Park Hospital, Countess of Chester Hospital and Leighton Hospital.

### **9.3.3. Ethical Approval**

Ethical approval for this trial was first granted from the research and development department at the base hospital, Royal Liverpool University Hospital, with the Royal Liverpool and Broadgreen University Hospitals NHS Trust acting as sponsor. Ethical approval was then granted from the regional ethics committee (North West REC centre). Once ethical approval was granted from both organisations, it was necessary to seek approval from the National Information Governance Board (NIGB) to gain section 251 approval under the NHS Act 2006. This would ensure that patient identifiable information

could lawfully be accessed and gathered for research purposes without explicit patient consent. It was not possible to seek patient consent due to the retrospective nature of the research. It would have been impossible to gain consent from all patients as a significant proportion would have either been lost to follow up or have died. Furthermore, in order to contact patients to gain consent for use of their information for research purposes their personal information would have to be accessed. This would have amounted to a breach of confidentiality in this 'catch-22' situation. The NIGB was a statutory body established to promote, improve and monitor information governance in health and adult social care. The Health Research Authority (HRA) and its Confidentiality Advisory Group (CAG) regarding section 251 applications have since absorbed its functions. Section 251 of the NHS Act 2006 "allows the Secretary of State for Health to make regulations to set aside the common law duty of confidentiality for defined medical purposes", in this case for medical research. Therefore, Section 251 approval was necessary so that the research could begin and progress. Section 251 approval was granted on the 17<sup>th</sup> April 2013.

#### **9.3.4. Inclusion/Exclusion Criteria**

##### Inclusion criteria:

Patients with a 'non-standard aneurysm' of their abdominal aorta who underwent repair within one of the centres listed above and within the above time period. Patients must have had a CTA of their abdominal aorta prior to the aneurysm repair that could be reviewed on a 3-dimensional workstation and be of satisfactory quality to allow for detailed anatomical measurements.

##### Exclusion Criteria:

All patients with previous surgical or endovascular repair of an abdominal aortic aneurysm were excluded. As well as any patients who were haemodynamically unstable or

undergoing repair for a leaking or ruptured aneurysm. Patients who underwent 'branched' endograft technology as opposed to fenestrated EVAR were excluded as this method of treatment is recognised to be entirely distinct from fEVAR and EVAR.

#### **9.3.5. Identification of patients**

Methods of patient identification were intentionally broad-based to maximise the likelihood of capturing all patients suitable for inclusion. Each hospital within the NHS records and documents procedures that patients undergo during an in-hospital stay; this information is used to support operational and strategic planning, resource utilisation, financial reimbursement and for research. In order to categorise and classify procedures that patients undergo a standardised classification system was developed in the 1980's, being further updated in the 1990's and then 2006. The classification was initially issued by the Office of Population Censuses and Surveys (OPCS). Every surgical procedure has a specific code attached to it termed the OPCS code.

The clinical coding team at the Royal Liverpool University Hospital was contacted and advice taken regarding the most suitable method of obtaining the desired information. After discussion with senior members of the clinical coding team a list of relevant OPCS codes (L18 – L28.9, Inclusive) were used to identify patients who were classed as having had an aneurysm repair. This resulted in a list of patients who had been 'coded' as having some form of aneurysm repair within the specified period. To identify further patients suitable for inclusion the intention was also to access theatre records of aneurysm repair, departmental databases and individual surgeon databases at each hospital.

Once patients were identified to be potentially suitable for inclusion their preoperative CT scan was reviewed to determine if their aneurysm was non-standard. Two reviewers independently reviewed the preoperative CT scan of each patient to assess the anatomical characteristics within the infrarenal neck. The CT scans were reviewed on a dedicated

workstation with software that enables 3-dimensional reconstruction of the CT scan which can be manipulated for close scrutiny (syngoMMWP; version: VE40A, Siemens, Munich, Germany). Each reviewer was experienced in the use of the workstation in reviewing CT scans, one was the chief-investigator (AM) and the other was the co-investigator (SRV). Each reviewer had the IFU for each stent-graft type available to refer to during scrutiny of each scan. The reviewer would be free to manipulate the images as they saw fit to perform the required measurements and come to a conclusion. If there was discordance between the opinions of the two reviewers regarding a specific patient, then that patient's CT scan was reviewed again by both reviewers and an agreement would usually be reached. If no agreement was reached, then the patient was not included in the study. Once reviewed, if the aneurysm was deemed non-standard then this patient was flagged as suitable for inclusion into the study.

Below is the identification process carried out for each vascular unit or hospital included in the research for non-standard aneurysm patients.

**Royal Liverpool Hospital:**

A list of 287 patients 'coded' as having had an aneurysm repair according to OPCS codes (L18 – L28.9) was retrieved from the hospital coding department. A further list of patients was retrieved from the hospital computerised theatre system that logs each operation done within the hospital. All vascular operations were retrieved from the 12-month period April 1<sup>st</sup>, 2007 - March 31<sup>st</sup>, 2008 returning 971 operation 'episodes'. A prospectively maintained departmental database of all endovascular procedures carried out during the entire study period was also scrutinised. Individual surgeon records from the National Vascular Registry, a personal online registry of all index operations, were also reviewed. The data entered into this registry is the responsibility of each individual surgeon. These lists were then crosschecked with duplicates and irrelevant patients (not receiving an

aneurysm repair) removed. There were 3 additional patients that were potentially suitable for inclusion that weren't captured in the initial search using OPCS codes, all from the theatre database. It was therefore decided that use of OPCS codes to identify patients was a reliable method of capturing most patients and this would be the primary method used at all other institutions, with theatre records scrutinised when possible to retrieve additional patients. A significant proportion of patients identified as potentially suitable for inclusion did not have a pre-operative CT scan available for review (65 patients). There were various reasons for this including; CT scan not performed, CT scan not available on computerised image review system (with hard copy of scan having been destroyed) and CT scan performed at another institution and therefore not available for review. For some cases where the CT scan was performed at another institution within the Cheshire and Merseyside region it was possible to transfer the CT images for review (6 patients) but in other cases the CT scan had been performed distant to the local region and images were not available for transfer. The remaining patients had their CT scan reviewed and were assessed to determine if they met the inclusion criteria.

**Aintree University Hospital:**

The coding department at Aintree University Hospital was contacted and a list of patients was retrieved using the same OPCS codes and dates as for the Royal Liverpool University Hospital (130 patients). Again, there were instances where it was not possible to review a pre-operative CT scan for the same reasons as stated above but where possible CT scans were transferred to the Royal Liverpool University Hospital for detailed review.

**Southport Hospital:**

The coding department at Southport hospital was contacted to supply a list of patients as in line with the above centres however a list could not be retrieved. There were difficulties in establishing lines of communication and this method of identifying patients was abandoned

from this hospital. Only two vascular surgeons were performing aneurysm repairs during the period specified. Therefore, each surgeon was contacted and provided a list of patients in whom they undertook elective aneurysm repair during the period specified. Endovascular aneurysm repair was not performed at Southport hospital. Relevant patients were identified for potential inclusion into the study (30 patients). A request was made to transfer the relevant preoperative CT scans for further review however hard copies of the films and digital records had been destroyed for the majority of the scans. This meant that only a small proportion of scans were transferred for further review (4 patients).

**Warrington Hospital:**

The coding department at Warrington hospital was contacted to supply a list of patients as in line with the above centres however a list could not be retrieved. There were difficulties in establishing lines of communication and this method of identifying patients from this hospital was abandoned. The clinical director of the vascular unit at Warrington hospital was contacted to provide a list of patients for the whole department. However, during the period of the data collection this vascular department was merged with another, meaning that there was no longer a permanent vascular surgery presence at this hospital. Lines of communication with the clinical director from this department also failed after the initial request for data and this method of identifying patients was abandoned from this hospital. An attempt was made to obtain a list of patients from the theatre database at this hospital, but the specified information was not available and therefore could not be transferred. It was therefore not possible to obtain a list of patients who underwent aneurysm repair from this institution, the process of trying to identify patients had taken greater than one year and it was decided due to time constraints that patient identification from this centre should be abandoned.

### **Arrowe Park Hospital**

The coding department at Arrowe Park hospital was contacted in the same manner as the above centres and a list of patients for the relevant time period was retrieved. The computerised reporting system was accessed at Arrowe Park Hospital, which contains written reports of scans and blood results. Using this system, relevant patients were identified for potential inclusion into the study. A request was made to transfer the relevant preoperative CT scans for further review however hard copies of the films and digital records had been destroyed for the majority of the scans. In the remaining cases, there was either delay in transferring the relevant scans or case notes were not available for review. This resulted in no patients being included in the final analysis from this centre.

### **Countess of Chester Hospital**

The coding department at Countess of Chester hospital was contacted in the same manner as the above centres and a list of patients for the relevant period was retrieved. To request for transfer of the CT scans to the Royal Liverpool Hospital, date of CT scan and pertinent patient information is required. Countess of Chester vascular department was contacted to enable access to this information, but lines of communication broke down after initial contact. It was therefore not possible to transfer any scans for review from this hospital and it was decided that patient identification from this centre should be abandoned.

### **Leighton Hospital**

The coding department at Leighton hospital was contacted in the same manner as the above centres and a list of patients for the relevant period was retrieved. During the period of study, the vascular unit at Leighton hospital had merged and centralised to another hospital meaning there was no permanent vascular presence at this site. This made retrieval of further information impossible as no lines of communication were open at this

hospital. Due to time pressures, it was decided that patient identification from this centre should be abandoned.

### 9.3.6. Outcome Measures

#### Primary Outcome Measures:

- 30-day mortality/In-hospital mortality
- Mid-term mortality and aneurysm related mortality
- Technical success
- Clinical Success

#### Secondary outcomes:

- Visceral vessel patency
- Renal insufficiency and need for dialysis
- Re-intervention rates, both surgical and endovascular
- Conversion to open repair
- Major complications

Of note, after the initial analysis, review and systematic review the outcome measure of clinical success was included as a primary outcome measure. In accordance with the reporting standards clinical success for endovascular repair is defined as successful deployment of the device without;

- Death as a result of aneurysm treatment
- Type I or III endoleak
- Graft infection or thrombosis
- Aneurysm expansion (diameter >5 mm, or volume >5%)
- Aneurysm rupture

- Conversion to open repair

The presence of stent-graft dilatation ( $\geq 20\%$ ), migration ( $\geq 5\text{mm}$ ), or failure of device integrity will class a case as clinical failure. For open repair success is dependent on the absence of aneurysm related death, graft infection or thrombosis and failure of device integrity. [93] No additional data was needed and all the information relevant to whether a case was a clinical success or not was gathered as part of the original study design. As can be seen clinical success effectively describes continued clinical efficacy across a broad range of outcomes throughout follow up and it was therefore decided it was an important and valid clinical outcome measure.

#### **9.3.7. Variables Measured**

Defined pre-operative and intraoperative variables were collected as well as detailed anatomical information about the patient's aneurysm. Information was collected from patient's case notes, laboratory results on hospital computer systems, computerised discharge summaries and clinic letters. A proforma was developed to assist with the data capture, however it was never used as data was recorded directly onto an excel spreadsheet in every case. Some patients who underwent endovascular aneurysm repair were also prospectively entered into an institutional database and where possible further information was retrieved from that database. In some cases, information on patients' whereabouts, date and cause of death were obtained by telephone contact with their last recorded general practitioner. Imaging studies and reports verified by radiologists were reviewed both pre-operatively and during follow up from the hospital computerised image review system. Pertinent data was recorded in a pseudoanonymised form, to comply with information governance principles and so that a reverse anonymisation process could be carried out later if further information was needed for a specific patient. All pseudoanonymised information was recorded in an excel spreadsheet. The data points that were recorded can be split into various categories as outlined below.

### **Demographic Variables:**

A variety of demographic information was collected for each patient included in the study. This information included the age and sex of the patient. If they were enrolled on an aneurysm surveillance programme prior to their aneurysm repair, the date of enrolment was also recorded.

### **Pre-operative Anatomical Characteristics of the Aneurysm:**

To obtain this information pre-operative CT scans were reviewed on the 3-dimensional workstation mentioned earlier, and all CT scans were reviewed on a single workstation. The software allows the reviewer to manipulate the images so measurements can be made in a plane orthogonal to the direction of blood flow. The aorta was reviewed in its entirety first then specific measurements were taken. Every CT scan was reviewed with the same settings for window width (800) and window level (100). The following protocol for anatomical measurements was designed after the chief investigator was trained in the use of the software and aortic CT measurements. The chief investigator was trained by a consultant vascular and endovascular surgeon working at the Royal Liverpool University Hospital. The methods for measurement were used by that consultant in his routine clinical practice and where necessary those methods were standardised to provide a reliable and reproducible way of measuring the anatomy. At the time of the design of the measurement protocol (early 2012) no comprehensive, validated and agreed protocol was found to exist from a search of the literature. Validated techniques pertaining to single anatomical variables existed. Measurements were obtained along a manually constructed central luminal line, without stretched vessel view. This was intentionally done to maintain the 3D structure of the anatomy in view when measurements were being made. All measurements were reviewed in at least 2 planes perpendicular to each other along the central luminal line (CLL), approximating a coronal and sagittal view, for lengths and angulation. Where necessary an axial view perpendicular to the central luminal line was used for

measurements such as diameter and assessment of thrombus and or calcification. Often all 3 views were interrogated for each parameter to ensure accuracy of measurement. All measurements were recorded on an excel spreadsheet. When any measurement herein refers to either the coronal or sagittal plane it most often was not a true anatomical coronal (or sagittal plane) as the image was manipulated to present what was felt to be the most accurate representation of the anatomy by studying the CT scan in numerous planes. Therefore, the image presented would be equivalent to an approximation of the coronal or sagittal planes not those actual planes in relation to standard anatomy teaching as they are offset to be orthogonal to the blood flow.

The measurements that were obtained and recorded included:

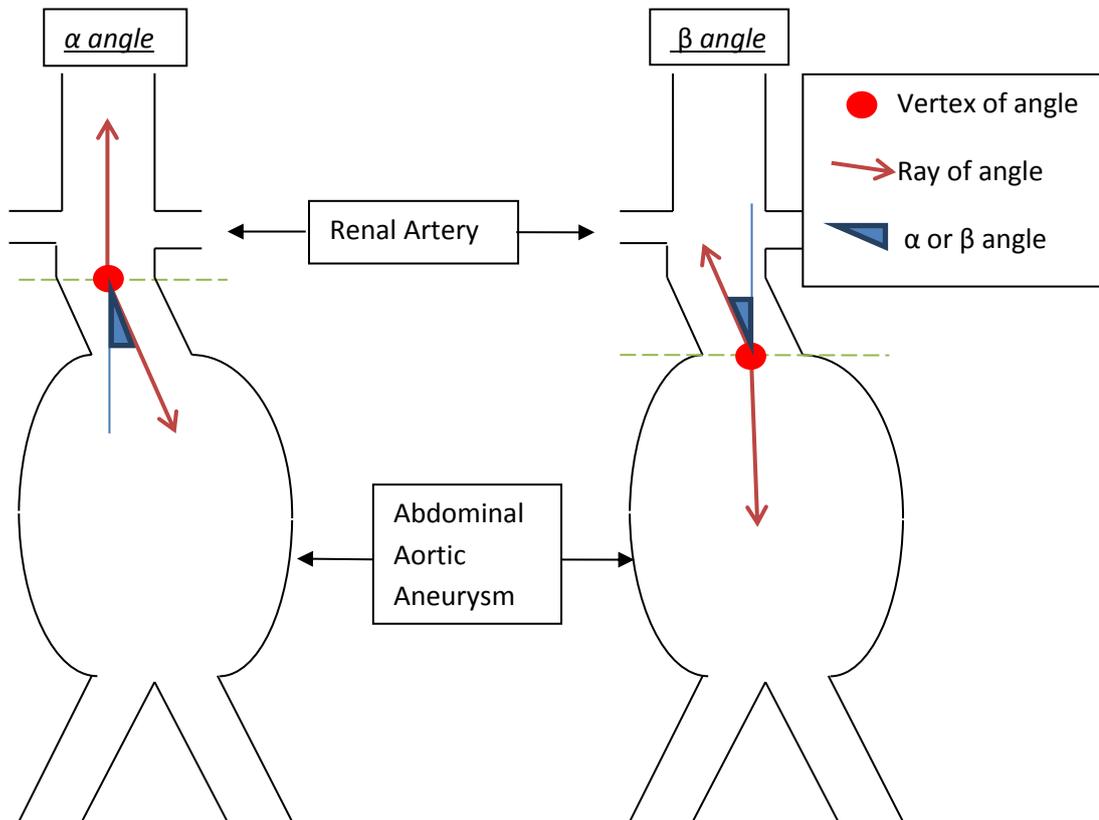
- Maximum aneurysm diameter – Measured at the widest point of the aneurysm from outer wall to outer wall. To obtain the measurement the aneurysm was inspected along the central luminal line in an orthogonal plane to the flow of blood. The axial sections were visually inspected to decide at which point was the widest and 2 measurements at 90 degrees to each other were taken from outer wall to outer wall. If there was significant discordance of these two measurements the process began again to ensure the image was as true as possible to the orthogonal plane as possible (an elliptical ‘slice’ of an aneurysm would give discordant values). This process was repeated at the investigator’s discretion at varying points if it was not immediately obvious where the largest diameter was. This was to ensure that the largest diameter was truly captured. If there continued to be discordance between two values because of an unusual shape of the aneurysm despite repeated measurements, an average of the two values was taken as the maximal diameter.

- Neck length – The lower border of the lowermost main renal artery to the top of the aneurysm was measured. If there was doubt about which point to take as the top of the aneurysm, for example when the neck is conical in shape, the point at which the aortic diameter increases by >10% compared with the diameter at the lower most renal artery was taken as the point at which the aneurysm began and the ‘neck’ ends. To determine the diameter for this purpose the neck was measured in the same way as described below for all neck diameter measurements.
- Neck diameter – This was measured outer wall to outer wall immediately below the lower border of the lowermost main renal artery and at 5, 10 and 15mm distal to this point. As with maximal aneurysm diameter two measurements were made at each level, 90 degrees to each other and intersecting the central luminal line. The 5, 10 and 15mm distance points were determined as the distance along the CLL from the lowermost renal artery. The “neck diameter” was taken as the largest measurement made at these 4 points unless any of the points were below the previously defined neck length (as defined above) and therefore the measurement was considered part of the aneurysm and not the neck.
- Neck angulation – Both the suprarenal aortic angulation and infrarenal aortic angulation were measured, termed the alpha ( $\alpha$ ) and beta ( $\beta$ ) angle respectively. A standardised method was developed to measure neck angulation as follows. Angulation was measured along the CLL. First the aneurysm was inspected, and the image rotated subjectively till the maximum angle for, first the alpha angle, then secondly the beta angle, was displayed in either the ‘sagittal’ or ‘coronal’ viewing box of the software. The image could be manipulated in any way to first identify the most angulated point and then

present it in either viewing box. The first point of angulation was determined visually by inspecting the visceral segment of the aorta in all 3 planes mentioned previously. These planes were manipulated in any way seen fit by the reviewer to determine where the first demonstrable angulation of the aorta occurred below the renal arteries. The vertex of the  $\alpha$  angle was placed at this subjectively determined point. If there was no clear demonstrable angulated point between the lowermost renal artery and the start of the aneurysm (which was previously determined as outlined above in neck length measurement) then the visceral aorta between the renal arteries and SMA was interrogated to determine if there was an appreciable angulation point in that segment of aorta. If there was then that point would be taken as the point of angulation and therefore the vertex of the angle placed at that point. If there was no obvious point of angulation between the SMA and the top of the aneurysm, then the point immediately below the lowermost renal artery was taken as the vertex. The vertex was always placed along the CLL. The rays of the angle were then placed along the long axis of the suprarenal aorta and the infrarenal neck. The angle calculated from this method was then subtracted from  $180^\circ$  to give the suprarenal aortic angulation with reference to the CLL – termed the  $\alpha$  angle. The vertex of the  $\beta$  angle is placed at the point of angulation immediately above the top of the aneurysm but below the vertex placed for the  $\alpha$  angle. If there is no such point, then the top of the aneurysm as previously defined would be the point at which the vertex for the beta angle was placed. One ray of the angle was along the long axis of the infrarenal neck exactly as in the  $\alpha$  angle and the second ray was along the long axis of aneurysm lumen, ultimately to the aortic bifurcation. The angle computed was again subtracted from  $180^\circ$  to give the  $\beta$  angle. (See Figure 7.1) Both angles

were measured in the 'coronal' and 'sagittal' planes. If either angle was outside of the IFU used for that patient, then they were considered to have a non-standard aneurysm.

*Figure 9.1 Method of Measuring  $\alpha$  and  $\beta$  Angles*



- Calcification within infrarenal neck – A subjective assessment was made as to the amount of calcification within the infrarenal neck, between the lowermost renal artery and top of the aneurysm. Although this area was the prime focus of the assessment the visceral segment of aorta would be interrogated too and an assessment of calcification within this segment would be made also. The degree of calcification was recorded as an ordinal variable; none, minimal, moderate or severe.

- Thrombus within infrarenal neck – Presence of thrombus was recorded within the infrarenal neck and where it was present a measurement was made as to the thickness of the largest burden of thrombus. The thickness of thrombus was measured from the inner aortic wall (intima) to the periphery of thrombus within the aortic lumen using the naked eye and subjective assessment. The circumference coverage of thrombus within the infrarenal neck was also estimated by subjective assessment.
- Patency of the visceral vessels – Each visceral vessel was noted and recorded whether it was patent or occluded due to whether it was opacified at its origin and remained so till its first branch. Any accessory renal arteries were noted and recorded but essentially ignored for the purposes of all the above measurements that refer to “the lowermost renal artery”.
- Expected clamp site – This was recorded as the site one would expect the aortic cross clamp to be placed if the patient were to hypothetically undergo open repair. For simplicity this was limited to infrarenal, suprarenal or supraceliac.

**Pre-operative Status of Patient:**

The data points that were collected are in part derived from validated risk prediction models designed specifically for patients undergoing major vascular surgery, namely the V-POSSUM. Details that were collected include; co-morbid conditions, ASA grade, objective tests for fitness for operation (Including spirometry, ECG and echocardiogram), subjective tests of fitness for operation (Including clinical examination of respiratory and cardiovascular systems) and blood tests (Including full blood count, urea and electrolytes).

**Intraoperative Details**

Intraoperative details collected were in part derived from recommendations for minimum reporting standards of endovascular aneurysm repair. These include length of operation,

blood loss, technical success, whether conversion to open repair took place, fluoroscopy time, total radiation dose and amount of contrast given. The use of planned or unplanned adjunctive procedures during the procedure was also recorded as well as patency of visceral vessels at end of operation.

### **In Hospital Complications**

All significant complications and reinterventions (including open and endovascular reinterventions) taking place within the first 30 days after operation or the total inpatient stay were recorded with details of event and outcome recorded as well. Laboratory investigations of renal function and need for dialysis in the short term was recorded.

### **Renal Function**

Hospital records and computerised results systems were interrogated to determine biochemical and clinical markers of renal function. This included serum creatinine levels, estimated glomerular function levels, documented urine output and the use of renal replacement therapy. Whenever available the estimated glomerular function calculated by the hospital laboratory was used for eGFR results. When there was no eGFR value calculated however the 2009 CKD-EPI creatinine equation was used to calculate the eGFR for a given creatinine value for individual patients. The equation is as follows: *2009 CKD-EPI creatinine equation:  $141 \min(SCr/k, 1)^a \max(SCr/k, 1)^{1.209} 0.993^{Age} [ 1.018 \text{ if female} ] [ 1.159 \text{ if black} ]$* , where *SCr* is serum creatinine (in mg/dl), *k* is 0.7 for females and 0.9 for males, *a* is 0.329 for females and 0.411 for males, *min* is the minimum of *SCr/k* or 1, and *max* is the maximum of *SCr/k* or 1.

In determining acute renal dysfunction in the post-operative period, the Kidney Disease: Improving Global Outcomes (KDIGO) definition was used to define whether a patient suffered an acute kidney injury during their hospital stay. The KDIGO definition also has a

staging system to enable severity of the acute kidney injury to be staged. The following table outlines criteria for the various stages of acute kidney injury using this system:

**Table 9.2. KDIGO staging of Acute Kidney Injury**

Stage	Serum Creatinine	Urine Output
<b>1</b>	1.5–1.9 times baseline OR $\geq 0.3$ mg/dl ( $\geq 26.5$ mmol/l) increase	< 0.5 ml/kg/h for 6–12 hours
<b>2</b>	2.0–2.9 times baseline	< 0.5 ml/kg/h for $\geq 12$ hours
<b>3</b>	3.0 times baseline OR Increase in serum creatinine to $\geq 4.0$ mg/dl ( $\geq 353.6$ mmol/l) OR Initiation of renal replacement therapy	< 0.3 ml/kg/h for $\geq 24$ hours OR Anuria for $\geq 12$ hours

With regards to chronic kidney disease the KDIGO definition of an abnormality of kidney structure or function which is present for > 3 months was used. The eGFR was used to define whether a patient had chronic kidney disease or not pre-operatively and during follow up after their operation. Chronic kidney disease was graded and categorised according to the system recommended by KDIGO. Patients with an eGFR of >60 were considered not to have chronic kidney disease. The CKD category for given eGFR values is as follows: eGFR 45 – 59 (category G3a), eGFR 30 – 44 (category G3b), eGFR 15 – 29 (Category G4), eGFR <15 (Category G5). The use of these definitions for both acute kidney injury and chronic kidney disease are recommended by The Renal Association in the UK.

**Mid-term follow up**

All significant complications and reinterventions (Including open and endovascular reinterventions) beyond the initial hospital stay were recorded with details of event and outcome recorded as well. Laboratory investigations of renal function, and whether there was any need for dialysis in the midterm was recorded.

### **Surveillance follow up**

All patients who undergo endovascular aneurysm repair have surveillance using a variety of imaging techniques. The most commonly applied surveillance protocol in the Cheshire and Merseyside region for standard EVAR is a plain abdominal radiograph (AXR) prior to discharge, one-month duplex ultrasound examination (DUS) and single arterial phase computed tomography scan (CTA). Annual AXR and DUS are then undertaken. The surveillance protocol for patients undergoing fEVAR is similar with the addition of AXR, DUS and CTA 6 months post operatively and CTA in addition to AXR and DUS annually. Patients who undergo open aneurysm repair do not have imaging surveillance but will occasionally undergo abdominal CT scans for either suspected aneurysmal/vascular pathology or entirely unrelated pathology. For all patients the verified report of each scan or x-ray was recorded with specific attention to any problems identified during the scan. In selected cases, the actual imaging was also reviewed, usually to confirm the findings mentioned in the report. Routinely during surveillance, the maximum aneurysm diameter is measured and the measurement from the DUS was recorded. If a DUS had not been performed but a CTA had then measurement would be taken from that. Measurement of aneurysm diameter was never taken from AXR as this is unreliable and often not possible. DUS was used as the principal method of obtaining maximum aneurysm diameter as this was available for the majority of patients during the total length of surveillance follow up who underwent endovascular repair. By contrast CTA was generally only available for patients who underwent fEVAR for the entire length of surveillance.

### **Mortality**

The date and cause of death was recorded where possible. Where there was no information relating to cause or date of death in the patient's hospital records other methods were used to attempt to clarify this information. The general practitioner was contacted to ascertain whether any information was available from their records as to the

cause or date of death. If this did not yield more information, then a request was made from the General Register Office for the death certificate.

### **9.3.8. Comparison of Non-Standard Patients with Standard Patients Undergoing EVAR or OR**

Above definitions, measurement protocol and type of variables measured was repeated for patients with a standard aneurysm undergoing EVAR or OR. This was designed to be a single centre retrospective study of all patients with standard aneurysm repair during the same study period defined above conducted at the base hospital the Royal Liverpool University Hospital and was intended to act as a control group for two of the treatment options OR and EVAR. From the retrospective multicentre study, a number of patients were identified as standard aneurysms. All of those that had their operation at RLUH were identified for inclusion into the single centre study. The method of patient identification used for the multicentre study was intentionally broad based to include all aneurysm repairs at any given centre and as such all patients identified as standard through that method reflect all standard patients operated on. To ensure full capture of all standard aneurysm patients happened with that method the local departmental database at the RLUH was cross checked again with the original list of patients identified as standard to ensure no patient was missed through the main search. That database is mentioned above and is a prospectively maintained database of all endovascular aneurysm repairs at the Royal Liverpool university Hospital. There is no such database for open aneurysm repairs and as such the identification of these patients was reliant on the above methodologies such as patients coded as having an aneurysm repair. The coding of aneurysm repair used in the above study would capture all aneurysm repairs regardless of their anatomy and therefore did not distinguish between standard and non-standard anatomy.

### 9.3.9. Comparison of Expected and Observed Mortality

The British Aneurysm Repair (BAR) Score is a published, validated model that provides an estimate of the risk of in-hospital mortality, expressed as a percentage, for patients undergoing elective aneurysm repair. [179] It was developed and validated using national audit data from the National Vascular Registry (NVR). The model uses 11 variables to calculate estimated in-hospital mortality for patients. These include; basic demographic variables (age and gender), results of blood tests (serum creatinine, sodium and white cell count), estimate of overall 'fitness' of the patient (ASA grade), previous medical history which may impact on the outcome (history of cardiac disease, whether the ECG is normal or abnormal), the extent of the proposed operation (open repair or EVAR, any previous aortic surgery), and finally one anatomic variable (AAA diameter). The variable of operation type only includes either EVAR or open repair within the BAR model. There is no distinction for fenestrated EVAR or non-standard open repair of aneurysm. This model was developed from a cohort of standard anatomy patients and this fact must be borne in mind when interpreting analyses that utilise it for a population of non-standard aneurysm patients.

The BAR score was used to compare the observed deaths with those that would be expected according to this model. Firstly, the BAR score was calculated for each patient. For those undergoing fEVAR the method of repair selected was 'EVAR'. If there were any missing data, then the lowest value available was selected for that variable with the exception of ASA grade. If the ASA grade was missing for any patient, then the mode of ASA grade for the rest of the cohort was used instead. This is in line with the published methodology on the use of the BAR score. To obtain the expected number of deaths the mean BAR score for each patient group (OR, EVAR and fEVAR) was calculated and then multiplied by the number of patients in that group. To compare the observed with expected deaths the Chi-square test with one degree of freedom was used. This procedure

was then repeated but the method of repair was reversed. In patients who underwent OR their BAR score was calculated as if they had had EVAR and vice versa.

#### **9.3.10. Risk Prediction Model**

To reiterate; the aim of this study was to compare clinical outcomes of conventional surgery, EVAR outside IFU and fEVAR for non-standard aneurysms. This research aim was developed to try and answer the question that the physician often faces when a patient presents with a non-standard aneurysm – ‘Which method of repair would be the best choice for my patient?’ To try to answer this supplementary question it would be important to try to develop a way of predicting risk for significant clinical events for a particular patient if they were to undergo one of the three proposed methods of aneurysm repair.

The decision to undertake the development of a risk prediction model specific to non-standard aneurysms was made following the beginning of data collection. This was because understanding of the research question developed through the data collection process and a deeper understanding of the applicability of the potential results of this study to a clinical scenario evolved. It was therefore concluded that if the data could be secondarily used to aid a physician in the decision-making process of which method of repair to use for a given patient then that would be beneficial and add to the overall conclusion of the analysis. The data collection was not primarily designed with this purpose in mind. However, it was felt there was no specific reason as to why the data already collected could not be used for this secondary purpose. With the proviso that its results should be interpreted with caution and would likely not be a complete risk prediction model but act as a basis to give a deeper understanding of what would be needed to develop a risk prediction model in future research.

In order to develop a risk prediction model univariate models were used to assess the relationship of different variables to survival time. The different variables assessed were;

age at operation, neck length, expected clamp site, ASA grade and method of repair undertaken. Further statistical modelling was used to assess the relationship between the variables mentioned above against primary technical success and clinical success. Initially it was intended to proceed with multivariate modelling however there was a limited number of significant clinical events recorded for each group and therefore this method of statistical analysis could not be undertaken as the results would have been unreliable.

### 9.3.11. Statistics

#### **Sample Size**

There was no accurate record of the number of aneurysm repairs or the proportion that were non-standard at the beginning of the study. An estimate of 500 – 600 patients was made for the two-year period from 1<sup>st</sup> April 2006 – 31<sup>st</sup> March 2008. It was estimated that roughly 150-200 [180] of these patients had a non-standard aneurysm. No power calculations or sample size calculations were done due to a lack of reliable pilot data.

#### **Analysis**

Non-standard aneurysms were grouped according to type of operation; open repair, EVAR or fEVAR. Continuous data is presented as median with range in parentheses. Overall survival and freedom from secondary intervention were subject to Kaplan-Meier analysis. Median follow up length was determined using the reverse Kaplan-Meier technique. SPSS version 20.0 (SPSS Inc, Chicago, Ill; www.spss.com) was used for all statistical analyses. If the patient was known to be alive and still on the surveillance programme their last point of follow up was taken as the point of data collection. If the patient was followed up elsewhere and hence not in the local programme, then their last point of imaging was taken as the last follow up time point.

## 9.4. Results

From an initial list of 494 patients, a total of 81 patients were confirmed to have a 'non-standard' aneurysm treated and therefore were eligible for inclusion in the final analysis. The following flow diagram shows how these patients were identified (See figure 9.2). As mentioned previously patients from only three centres were included because patient data was not available from the other four. These three centres were the Royal Liverpool University Hospital, Aintree University Hospital and Southport Hospital.

Figure 9.2 Flow Diagram of Numbers of Patients

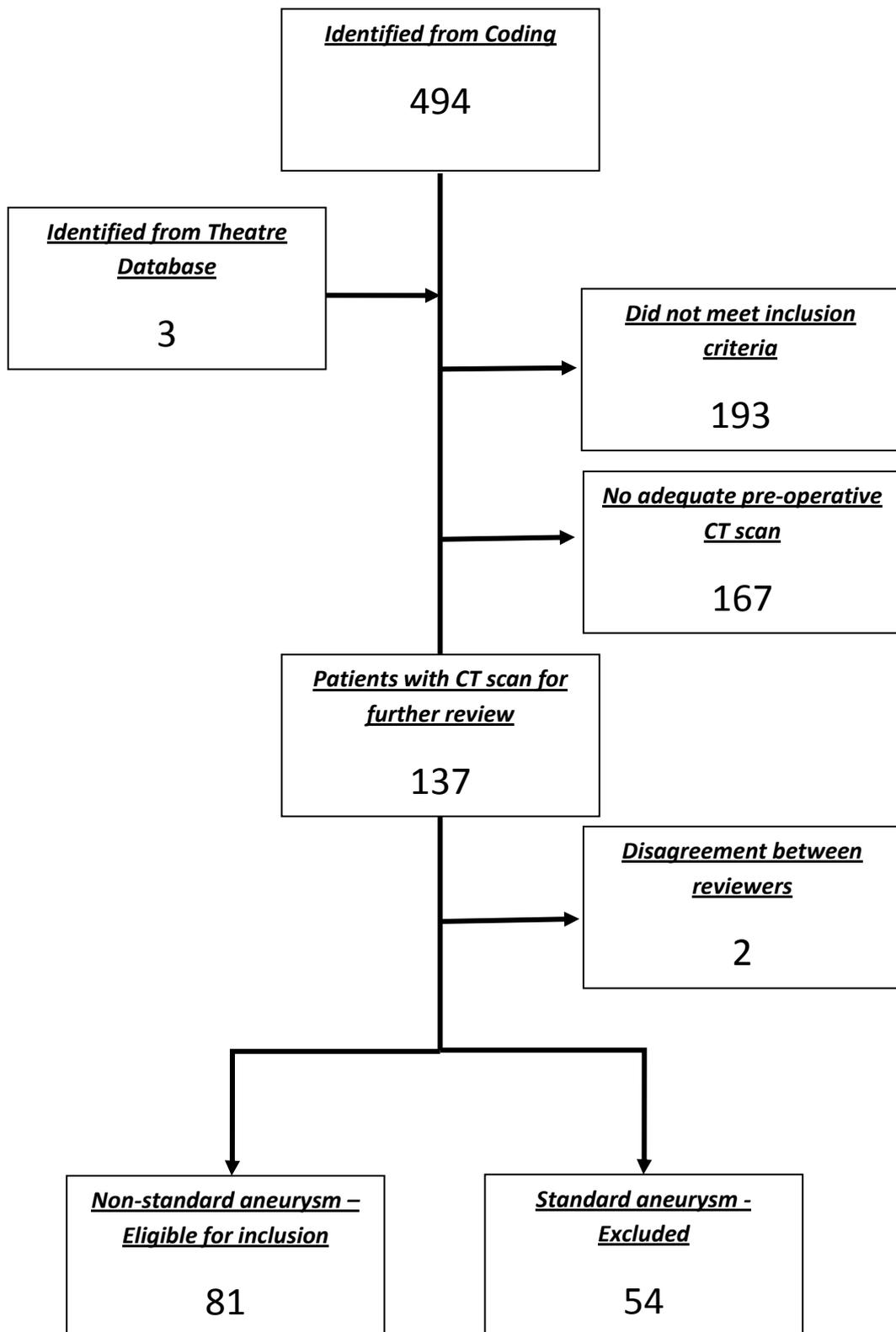


Figure 9.2 - Numbers represent patients. Arrows denote whether patients were excluded or included.

Patients were excluded from the final analysis for various reasons in accordance with the inclusion and exclusion criteria. The most common reasons a patient was excluded from further analysis were: presence of a ruptured aneurysm, a small (<55mm maximal aneurysm diameter) AAA was treated, the operation was given the incorrect OPCS code and in fact the patient never received an aneurysm repair, and the aneurysm was thoracoabdominal. Other less common reasons for exclusion were patients that had previously undergone an abdominal aortic aneurysm repair prior to the study period and patients with no clinical information retrievable. It should be noted that a large proportion of exclusions were due to the fact that an adequate pre-operative CT scan was not available for review.

In nine cases there was initial disagreement between the two reviewers as to whether the aneurysm was non-standard or not. After secondary review an agreement was reached in seven patients (six non-standard aneurysms and one standard aneurysm). This meant that two patients were excluded from further analysis as no inter-observer agreement could be reached. Cohen's  $\kappa$  was run to determine the strength of agreement between the two reviewers as to whether an aneurysm was standard or non-standard, Cohen's  $\kappa = 0.969$  (95% CI, 0.928 to 1),  $p < 0.0001$ . The strength of agreement between the two reviewers' judgements therefore was very good. [181] In fact the strength of agreement between the two reviewers remains very good even when only considering the first round of review, Cohens  $\kappa = 0.859$  (95% CI, 0.770 to 0.948),  $p < 0.0001$ .

Descriptive statistics were computed for the entire study population. Continuous variables are presented as their medians and inter-quartile ranges (IQR). Categorical variables are presented as counts and percentages. Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry.

A total of 81 patients were identified as being eligible for inclusion in the analysis. This included 37 patients that underwent open repair (OR), 15 patients who underwent fenestrated endovascular aneurysm repair (fEVAR) and 29 patients who underwent standard endovascular aneurysm repair (EVAR). Of the 29 patients who underwent standard EVAR 28 patients received a stent-graft from the Zenith Flex (Cook Inc. Bloomington, Indiana) platform and one patient received an Aorfix device (Lombard Medical Inc. Oxfordshire, UK). The Aorfix device does not have any suprarenal fixation and exhibits different characteristics and IFU criteria than the Zenith Flex device. All patients who underwent fEVAR received the Zenith Fenestrated (Cook Inc. Bloomington, Indiana) platform which is made by the same company and indeed the device itself is based on the Zenith platform in general. It was therefore decided that the one patient who was treated with the Aorfix device represented an outlier in terms of device used and was excluded from the final analysis. The original intention in the design of the study was to include all patients identified as non-standard irrespective of stent graft device used and thereby excluding this one patient raises the potential for statistical bias in the results and therefore this should be borne in mind when interpreting the following results.

#### **9.4.1. Pre-operative Variables**

##### **Demographics**

A total of 80 patients were included in the final analysis and their results are presented below. These patients underwent treatment of their abdominal aortic aneurysm between May 2006 and March 2008. A total of 28 patients underwent treatment with standard EVAR (EVAR), 15 with fenestrated EVAR (fEVAR) and 37 patients underwent abdominal aortic aneurysm repair as an open procedure (OR). The majority of patients were male (67.5%) and the median age was 75 (68 - 81). The following table details the demographics

for all the patients grouped according to the type of operation performed and as a total for the whole group. (See table 9.2)

**Table 9.3 Patient Demographics**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	p-value
Age at operation (years), median (IQR)	79 (73, 84)	71 (65, 81)	74 (67, 78)	75 (68, 81)	0.052
Sex, n (%)					0.053
Male	21 (75.0)	13 (86.7)	20 (54.1)	54 (67.5)	
Female	7 (25.0)	2 (13.3)	17 (45.9)	26 (32.5)	
Previous Abdominal Surgery, n (%)					0.474
Yes	5 (17.9)	5 (33.3)	7 (18.9)	17 (21.3)	
No	23 (82.1)	10 (66.7)	28 (75.7)	61 (76.3)	
Unknown	0	0	2 (5.4)	2 (2.5)	
IHD, n (%)					<b>0.001</b>
No	15 (53.6)	2 (13.3)	24 (64.9)	41 (51.3)	
Yes	12 (42.9)	13 (86.7)	11 (29.7)	36 (45.0)	
Unknown	1 (3.6)	0 (0.0)	2 (5.4)	3 (3.8)	
COPD, n (%)					0.472
No	22 (78.6)	10 (66.7)	28 (75.7)	60 (75.0)	
Yes	6 (21.4)	5 (33.3)	6 (16.2)	17 (21.3)	
Unknown	0 (0.0)	0 (0.0)	3 (8.1)	3 (3.8)	
CVA, n (%)					0.540
No	24 (85.6)	12 (80.0)	32 (86.5)	68 (85.0)	
Yes	2 (7.1)	3 (20.0)	3 (8.1)	8 (10.0)	
Unknown	2 (7.1)	0 (0.0)	2 (5.4)	4 (5.0)	

<b>DM, n (%)</b>					0.890
No	25 (89.3)	13 (86.7)	32 (86.5)	70 (87.5)	
Yes	3 ( 10.7)	2 (13.3)	3 (8.1)	8 (10.0)	
Unknown	0 (0)	0 (0.0)	2 (5.4)	2 (2.5)	
<b>PVD, n (%)</b>					1.000
No	23 (82.1)	12 (80.0)	29 (78.4)	64 (80.0)	
Yes	5 (17.9)	3 (20.0)	7 (18.9)	15 (18.8)	
Unknown	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.3)	
<b>Hypertension, n (%)</b>					0.309
No	7 (25.0)	6 (40.0)	7 (18.9)	20 (25.0)	
Yes	20 (71.4)	9 (60.0)	29 (78.4)	58 (72.5)	
Unknown	1 (3.6)	0 (0.0)	1 (2.7)	2 (2.5)	
<b>ASA Grade, n (%)</b>					0.038
1	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.3)	
2	5 (17.9)	3 (20.0)	16 (43.2)	24 (30.0)	
3	20 (71.4)	12 (80.0)	15 (40.5)	47 (58.8)	
4	3 (10.7)	0 (0.0)	1 (2.7)	4 (5.0)	
Unknown	0 (0.0)	0 (0.0)	4 (10.8)	4 (5.0)	

Table 9.3 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry. IHD = Ischaemic Heart Disease. COPD = Chronic Obstructive Pulmonary Disease. CVA = Cerebrovascular Accident. DM = Diabetes Mellitus. PVD = Peripheral Vascular Disease. ASA= American Society of Anesthesiologists Grade.

Concerning pre-operative comorbidities, only the incidence of ischaemic heart disease was found to be significantly different between the three groups undergoing aneurysm repair. A significantly higher proportion of the patients who underwent fEVAR exhibited a history of ischaemic heart disease when compared with OR or EVAR. Only one patient (within the

OR group) had suffered an acute coronary syndrome within the 6 months prior to their aneurysm repair. That patient suffered no further acute coronary syndrome post operatively or at all during the follow up period.

ASA (American Society of Anesthesiologists) grade was not statistically different across the three types of operation. A higher proportion of patients undergoing open repair, however were deemed to have a lower ASA grade (<3) pre-operatively (45.9%) compared with those undergoing EVAR (17.9%) and fEVAR (20%).

In addition to the above preoperative variables information was also collected with regards to smoking status and medications prescribed (antiplatelet, statin, angiotensin converting enzyme (ACE) inhibitor,  $\beta$ -blocker and steroid). There was no statistical difference between the smoking statuses of the patients. There were also no statistically significant differences between the proportions of patients taking the above medications across the three types of operations. The majority of patients were prescribed an antiplatelet agent (66%) and a statin (69%).

#### **Pre-operative investigations**

Parameters derived from pre-operative investigations were also collected for each patient. No statistically significant differences were found between the three groups with regards to pre-operative renal function or pre-operative values obtained from spirometry testing (See table 9.4). No patient was noted to be on renal dialysis pre-operatively and chronic kidney disease, as defined as having an eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$ , was present in 45% of all patients. Only 15% of all patients were noted to have an abnormal creatinine pre-operatively ( $>130\ \mu\text{mol}/\text{L}$ ). The distribution of patients with abnormal renal function by either abnormal creatinine or a presence of chronic kidney disease was not statistically significant across the three types of repair.

**Table 9.4 Pre-operative Investigations**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	p-value
<b>Best FEV1, median (IQR)</b>	1.9 (1.5, 2.2)	2.3 (1.7, 2.6)	2.0 (1.5, 2.6)	1.9 (1.6, 2.6)	0.778
Unknown (%)	4 (14.3)	2 (13.3)	6 (16.2)	12 (15.0)	
<b>FEV1/FVC Ratio, median (IQR)</b>	66.8 (58.7,73.7)	70.5 (64.5,74.4)	70.4 (65.3,77.2)	69.5 (60.5,74.7)	0.558
Unknown (%)	4 (14.3)	2 (13.3)	7 (18.9)	13 (16.3)	
<b>Creatinine (µmol/L), Median (IQR)</b>	97.0 (87.0, 118)	88.0 (81.0, 115)	95.0 (78.0, 108)	94.0 (81.0, 114)	0.249
<b>eGFR (ml/min/1.73m<sup>2</sup>), median (IQR)</b>	59.2 (46.3,72.7)	72.8 (49.6,81.7)	63.4 (47.7,72.7)	63.2 (48.4,75.7)	0.341
<b>Chronic Kidney disease, eGFR &lt;60</b>					
None, eGFR ≥60 (%)	13 (46.4)	9 (60)	22 (59.5)	44 (55)	
Category 3a, eGFR 45 – 59 (%)	8 (28.6)	3 (20)	9 (24.3)	20 (25)	
Category 3b, eGFR 30 – 45 (%)	6 (21.4)	3 (20)	5 (13.5)	14 (17.5)	
Category 4, eGFR 15 – 29 (%)	1 (3.6)	0 (0)	1 (2.7)	2 (2.5)	

Table 9.4 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher’s exact test or  $\chi^2$  test, depending on the amount of data present in each entry. FEV1 = Forced expiratory volume in one second. FVC = Forced Vital Capacity. eGFR = Estimated Glomerular Filtration Rate.

Information was also collected about preoperative cardiac investigations. Patients were assessed on an individual basis and as such some had preoperative dynamic imaging of the heart, such as transthoracic echocardiogram, multi-gated acquisition scan (MUGA), dobutamine stress echocardiogram (DSE) or a myocardial perfusion scan (using methoxy-isobutyl-isonitrile, MIBI), and some simply had no pre-operative imaging. A significant proportion (41.3%) of patients had no assessment of their ejection fraction pre-operatively. 47 patients had a documented assessment of their left ventricular function (LVF) preoperatively and the majority of those (27 patients, 57%) were patients undergoing open repair. Of eleven patients undergoing EVAR who had a documented LVF preoperatively, 1 patient was found to have “significant” impairment of their LVF with the remainder being “normal”. Of nine fEVAR patients, one had “mild” impairment, one had “mild-moderate” impairment and the remainder were “normal. Of the 27 patients undergoing open repair three had “mild impairment” and the remainder were normal. Six patients were found to have mild valvular abnormalities, but no patient was found to have moderate or severe aortic valve stenosis or regurgitation. Most patients, 73 (91.3%), had an electrocardiograph (ECG) preoperatively, with 17 (23.3%) of those found to have an abnormality on their ECG. The following abnormalities were detected on the pre-operative ECG: atrial fibrillation (6 patients), Sinus bradycardia (4 patients), Left axis deviation (2 patients), right bundle branch block (2 patients), type 1 atrioventricular block (1 patient), t-wave inversion (1 patient) and q waves (1 patient).

#### **9.4.2. Primary Outcome Measures**

The primary outcome measures were:

- In-hospital mortality
- Mid-term overall survival
- Mid-term aneurysm related mortality
- Technical success

- Clinical success

### **In Hospital Mortality**

Four patients died before being discharged from hospital (5% in hospital mortality). Two patients had standard EVAR (7.1% in hospital mortality) and two patients had OR (5.4% in hospital mortality) (p= 0.823).

The first EVAR patient was a 91-year-old woman who underwent a lengthy EVAR procedure. There were no significant immediate complications, but she returned to theatre on day 8 because of a gastric perforation. She survived the operation but deteriorated after that and eventually died on the 14<sup>th</sup> post-operative day. Her cause of death was certified as sepsis secondary to gastric perforation (operated). The second EVAR patient was an 85-year-old gentleman who was deemed to be ASA grade 4 with a significant cardiac history. He suffered significant blood loss during the operation (2500mls) and was haemodynamically unstable on the critical care unit postoperatively. He required multiple blood transfusions and cardiovascular support with infusion of inotropic medication. He developed gastrointestinal obstruction and was palliated on day 19 post operatively. He died on the 23<sup>rd</sup> post-operative day.

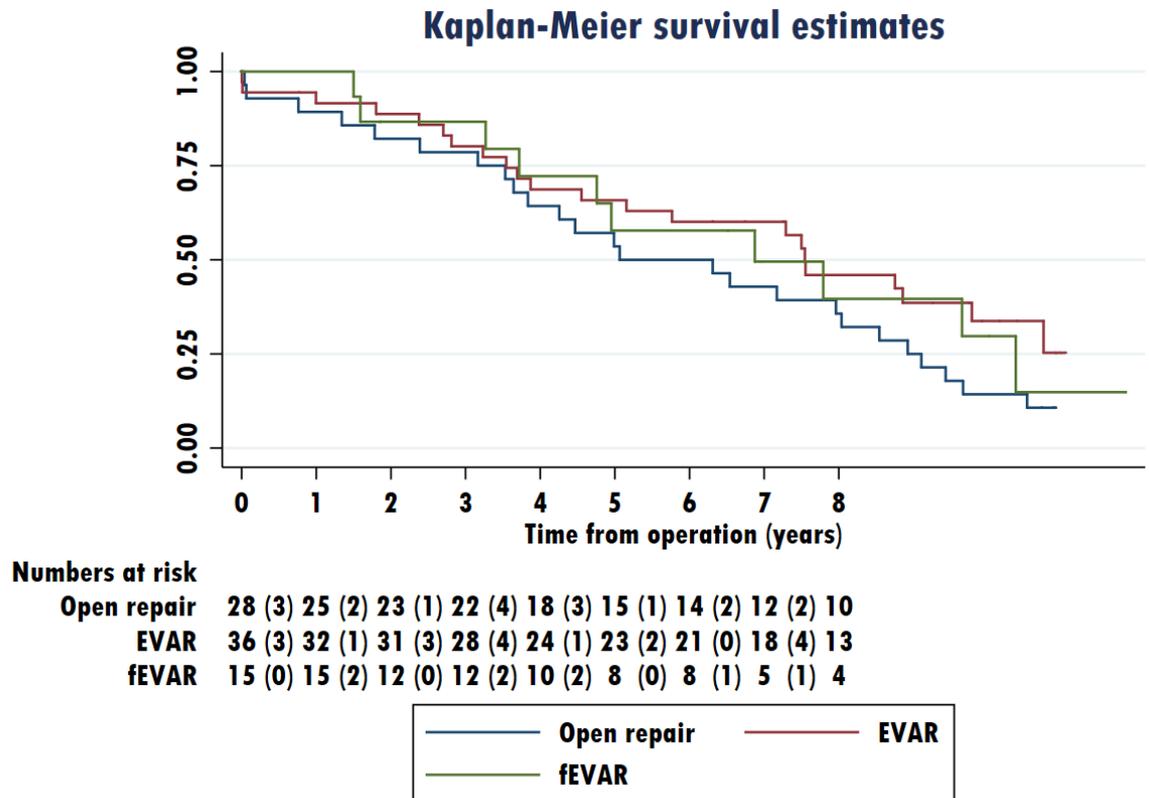
The first OR patient who died during the index hospital admission was a 91-year-old man who had a prolonged operation with significant blood loss (3000mls), he required 2500mls of blood transfusion intraoperatively. On the first day after the operation, he had deranged clotting factors, ischaemic changes on his ECG and increasing inotropic requirement on the intensive care unit. He died later that day. The second OR patient was a 71-year-old man with a significant cardiac history who also suffered significant blood loss (2000mls). On the second postoperative day, he suffered a sudden myocardial infarction and cardiac arrest; the patient had return of spontaneous circulation for a short time but died later that day.

### **Overall Survival**

To determine the follow up time for the whole cohort the 'reverse Kaplan-Meier' methodology was used, [182]with the median follow up being 10.72 years (95% CI 9.74 – 10.91). Separately for the three repair groups the median follow up (with 95% confidence intervals) in years is as follows: fEVAR 10.02 years (6.96 – NA), EVAR 10.88 (10.77 – NA), Open Repair 9.92 (8.76 – 10.91). A total of 57 patients died during the study period (25 EVAR patients, 10 fEVAR patients and 22 OR patients). Kaplan-Meier survival curves were generated in order to have a graph that compares the survival functions between the three surgery types and also a table showing the number of patients at risk (see figure 9.3 below). Overall survival at 5 years was ; 54% (15 out of 28 patients) for EVAR, 57% (8 out of 14 patients) for fEVAR and 68% (25 out of 37 patients) for Open Repair. For the whole cohort 29% of patients (n=22) survived to 10 years. And 24% patients (n=19) were alive at the end of the study period.

Event of interest was death. Patients that until last follow-up were alive were treated as censored. Patients with missing data for death date and last visit date were excluded (1 patient). Total number of observations included: **N=79**

Figure 9.3: K-M survival estimates with failure events (deaths) indicated in brackets



A log-rank test was performed in order to compare those independent groups of survival time. The log-rank test is a non-parametric method for testing the null hypothesis that the groups being compared are samples from the same population as regards survival experience. Table 9.5 indicates a non-statistically significant p-value ( $=0.283 > 0.017$ ) at a statistically significance level  $\alpha=1.67\%$  (Bonferroni correction). In other words, there is no evidence to suggest a statistically significant difference between the survival experiences of patients amongst the three methods of repair.

*Table 9.5: Shows the results of the log rank test comparing survival distributions by surgery type*

Surgery Type	Events Observed	Events expected
Open repair	22	27.06
EVAR	25	19.50
fEVAR	10	10.44
Total	57	57.00
	Chi2(2) = 2.53	
	Pr>chi2 = 0.283	

Life tables reporting survival rates were also produced indicating that:

80% of patients survived 3 years or more in the open repair group. The percentage of patients surviving 7 years and above was 60% (see table 9.6).

In EVAR group (see table 9.7), 79% of patients survived 3 years or more while 42% survived 7 years and above.

In fEVAR group (see table 9.8), 87% of patients survived 3 years or more, while 50% of patients survived 7 and above years.

*Table 9.6.: Survival Rates for Open Repair (n<sub>1</sub>=36)*

Time	Survival rate	95% Conf. Interval
3 follow-up years	80%	[63% to 90%]
7 follow-up years	60%	[42% to 74 %]

*Table 9.7: Survival Rates for EVAR (n<sub>2</sub>=28)*

Time	Survival rate	95% Conf. Interval
3 follow-up years	79%	[58% to 90%]
7 follow-up years	42%	[25% to 60%]

*Table 9.8.: Survival Rates for fEVAR (n<sub>3</sub>=15)*

<b>Time</b>	<b>Survival rate</b>	<b>95% Conf. Interval</b>
3 follow-up years	87%	[56% to 96%]
7 follow-up years	50%	[22% to 72%]

**Aneurysm Related Mortality**

The exact cause of death was not available for 16 patients. A meaningful analysis of aneurysm related mortality could therefore not be performed. In addition to the two in hospital deaths for each of the EVAR and OR groups there was a further one death during follow up in each group that was aneurysm related. The details of each case are outlined below:

- EVAR patient:
  - 15 months post EVAR – Caudal migration diagnosed on plain AXR, CTA organised
  - 18 months post EVAR – Type 1a endoleak diagnosed, with complete loss of proximal seal, Conversion to open repair planned.
  - 22 months post EVAR – Died secondary to a ruptured aneurysm before undergoing open repair
- OR patient:
  - 4 years post OR – Empyema of the gallbladder, subsequent cholecystectomy
  - 5 years post OR – Multiple episodes of sepsis, prosthetic graft infection diagnosed, and long-term antibiotics started
  - 6 years post OR – Presented with acute gastrointestinal bleeding secondary to an aortoenteric fistula. Died as a result of massive haemorrhage

**Technical Success**

The following table demonstrates the proportions of patients that exhibited technical success. (See table 9.9)

**Table 9.9 Technical Success**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
<b>Technical Success, n (%)</b>					<b>&lt;0.001</b>
No	7 (25.0)	2 (13.3)	1 (2.7)	10 (12.5)	
Yes	21 (75.0)	13 (86.7)	36 (97.3)	70 (87.5)	

Table 9.9 - Comparison categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry

When comparing the proportion of technical success, there was a statistically significant difference in the proportions of patients exhibiting technical success. There were seven cases of technical failure in the EVAR group for the following reasons:

- Four cases of persistent type 1a endoleak at the end of the procedure
- Three cases of unplanned endovascular procedures – two were patients with a limb kink necessitating placement of further stents within the iliac limb and one case of an unplanned palmaz cuff extension to treat a type 1a endoleak (successful).

This means that assisted primary technical success was present for 24 (85.7%) patients in the EVAR group. If comparing this success rate for EVAR with the other two treatments, there was no longer a statistically significant difference. Of the four cases of persistent type 1a endoleak: One patient had no further type 1a endoleak identified during the follow up and died approximately nine years postoperatively from non-aneurysm related cause. Three patients had a type 1a endoleak identified at some point during the follow up:

- One was only seen on the one-month surveillance scan and never again, patient died of unknown cause nearly five years after the original operation.
- One patient had migration and further type 1a endoleak identified and successfully underwent a conversion to open repair within the first year after their index operation. The patient recovered well and remained alive for approximately 10 years until their death of unknown cause.
- The final patient had migration and type 1a endoleak noted but died from a ruptured aneurysm prior to conversion to open repair.

Adjusting the assisted primary technical success to take further account of the two above patients in whom their type 1a endoleak did not persist and did not cause any demonstrable deleterious effects gave an “adjusted” rate of 92.9% for EVAR.

There were two patients with technical failure in the fEVAR group, both secondary to a modular type 3 endoleak, between the connection of renal stent and main stent-graft body noted at the end of the procedure. Both patients were treated intraoperatively with balloon moulding of this connection zone, which reduced but did not abolish the endoleak. It was decided to treat these conservatively with close follow up in surveillance. Neither patient exhibited a graft related endoleak at any point during the rest of their follow up. One patient died from non-aneurysm related cause nearly five years after the original procedure and the other was alive at the last surveillance time point.

The one case of technical failure within the open group was a patient who died within the first 24 hours post-operatively, in line with reporting standards this is deemed a technical failure. [93]

### **Clinical Success**

In accordance with the reporting standards clinical success for endovascular repair is defined as successful deployment of the device without;

- Death as a result of aneurysm treatment
- Type I or III endoleak
- Graft infection or thrombosis
- Aneurysm expansion (diameter >5 mm, or volume >5%)
- Aneurysm rupture
- Conversion to open repair

The presence of stent-graft dilatation ( $\geq 20\%$ ), migration ( $\geq 5\text{mm}$ ), or failure of device integrity will class a case as clinical failure. For open repair success is dependent on the absence of aneurysm related death, graft infection or thrombosis and failure of device integrity. [93]

There were 17 (21.3%) cases of clinical failure; 13 in the EVAR group, one in the fEVAR group and 3 in the OR group. This difference reached statistical significance ( $p < 0.001$ ).

In the EVAR group, the mode of failure was:

- Migration (3 patients)
- Open conversion (3 patients)
- Migration and aneurysm expansion (2 patients)
- Migration and type 1 endoleak (1 patient)
- Expanding aneurysm (1 patient)
- Type 1 endoleak (1 patient)
- In hospital death (2 patients)

In the fEVAR group, the mode of failure was:

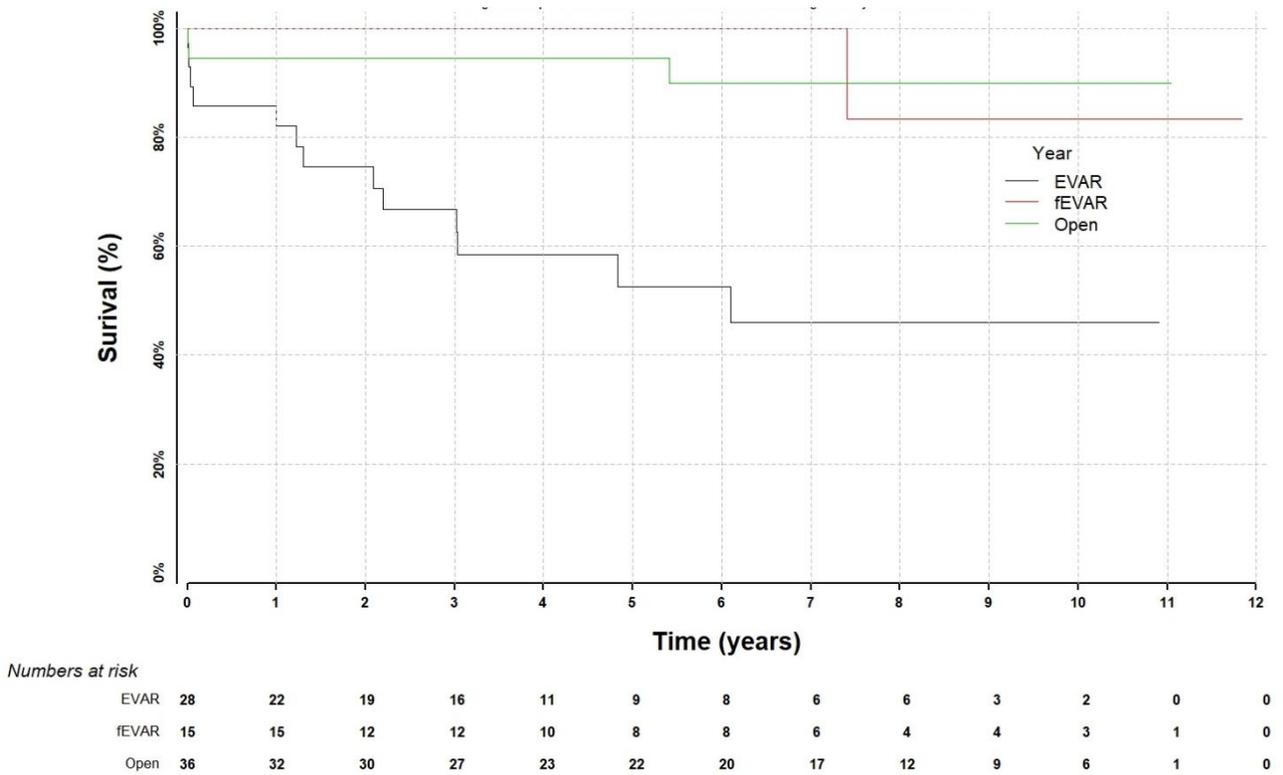
- Expanding aneurysm (1 patient)

In the OR group the mode of failure was:

- Graft infection and aneurysm related mortality (1 patient)
- In hospital death (2 patients)

The following graph demonstrates freedom from clinical failure for the three treatment options over the course of follow up as analysed by the Kaplan Meier method (See figure 9.4.)

*Figure 9.4: K-M survival estimates with failure events (clinical failure)*



Of those patients with clinical failure the 3 OR patients died as a result of their clinical failure. The fEVAR patient had a recorded expansion of aneurysm 86 months after the initial procedure. The patient had expansion from 47mm to 53mm and a type 2 endoleak

After this no endoleak was noted and at last surveillance scan the aneurysm measured 59mm without secondary intervention and without endoleak, the patient remains alive on the surveillance programme. Of the 13 EVAR patients; 6 either died as an inpatient, had an open conversion or suffered a ruptured aneurysm (1 patient). The remaining 7 patients are detailed below:

- Type 1 endoleak (1 month, IFU violation: Conical, B angle 70 degrees)
  - Endoleak never seen again, no intervention and shrinking aneurysm without endoleak on last surveillance scan before death from other causes
- Migration (15 months, IFU violation: Conical)
  - No intervention, shrinking aneurysm at last surveillance scan without endoleak. Patient died from non-aneurysm related causes.
- Migration (25 months, IFU violation: Neck diameter 37mm, Conical, Thrombus)
  - Patient still alive on surveillance programme with shrinking aneurysm, no endoleak and no secondary intervention at last follow up.
- Migration (26 months, IFU violation: Neck length 7mm)
  - Patient had migration noted at 26 months, on last surveillance scan patient had neck dilatation noted with very limited seal proximally but no identifiable endoleak. The patient was diagnosed with metastatic cancer within liver and bone from unknown primary 1 month after this scan and died secondary to the malignancy 2 months after that diagnosis.
- Migration and Expanding Aneurysm (36 months, IFU violation: Conical, Thrombus)
  - Patient had migration noted at 36 months post op, then aneurysm was noted to be shrinking with no endoleak identified from 59mm to 50mm. Without endoleak the aneurysm then was noted to be 56mm classifying it as an expanding aneurysm. The measurement of 50mm was one isolated scan and raises the possibility of measurement error. Regardless the

patient continued to exhibit migration and on the final surveillance scan was noted to have a proximal endoleak that could not be defined as either type 1 or 2. This was 3 years after the migration was first noted. The patient died of non-aneurysm related causes on review of clinical case notes 3 months later. (Pneumonia and Myocardial infarction)

- Migration and Expanding Aneurysm (57 months, IFU violation: thrombus alone)
  - This patient had a 77mm diameter AAA treated, the neck diameter was measured at 30mm immediately below the renal arteries but then was 27 and 26mm at 5, 10 and 15mm below the renal arteries. A 30mm diameter stent graft was placed in this 21mm long neck. Migration expanding aneurysm was noted with very little seal in proximal neck but no identifiable endoleak. The patient underwent a cuff extension 60 months from the original procedure with a chimney renal stent. The patient recovered well from the operation and the last surveillance scan revealed the aneurysm was continuing to expand and was now 110mm in size but with no identifiable endoleak on contrast enhanced ultrasound. The patient died from non-aneurysm related causes after this.
  
- Expanding Aneurysm (73 Months, IFU violation: Alpha angle 47 deg, Beta angle 62 degrees)
  - This aneurysm was noted to be shrinking with no concerns to 39mm up to 73 months then expanded to 45mm, 53mm and 55mm on subsequent surveillance scans. No endoleak or loss of proximal seal was noted. No intervention was performed. The patient died from non-aneurysm related causes 3 years after aneurysm expansion was first noted.

The above cases of clinical failure highlight a few things. Although the definition of clinical failure is appropriate to include all the above patients the difficulty of static definitions

applied to patients experiencing longitudinal surveillance is highlighted – for example the patient who exhibited an endoleak at the 1-month surveillance point and then never again was classed as clinical failure at that point and forever more. Despite the fact no identifiable sequelae came from this “clinical failure” identified at one surveillance time point. Furthermore, there were 2 patients in whom migration was noted and therefore classed as clinical failure but then stabilised and needed no intervention and had shrinking aneurysms throughout the remainder of their follow up. Although these three patients meet the definition of clinical failure, they do not clearly exhibit features that would be considered a clinical failure. The cases above also highlight that clinical failure may occur at any point throughout follow up even beyond 5 years, highlighting the importance of continued surveillance for these patients. Finally, the cases demonstrate that although clinical failure may occur it is not mandatory to treat the clinical failure at all costs because clearly these aneurysm patients have a high mortality rate from non-aneurysm related causes and interventions may not alter the clinical course for a given patient. The difficulty of course in this regard is that it is not clear which patients will go on to suffer aneurysm related mortality secondary to their clinical failure or not. This would be an important area for further research to determine if there are any predictive factors regarding clinical failure that can stratify patients into high or low risk.

### **9.4.3. Secondary Outcome Measures**

The secondary outcome measures were:

- Visceral vessel patency
- Renal insufficiency and need for dialysis
- Re-intervention rates, both surgical and endovascular
- Conversion to open repair
- Major complications

### **Visceral vessel patency**

Throughout the follow up period, only one visceral vessel was recognised to have occluded. One patient in the EVAR group suffered occlusion of their left renal artery secondary to maldeployment of the stent-graft during the procedure resulting in coverage of the renal artery. The patient suffered a temporary rise in their creatinine post-operatively exhibiting stage 1 acute kidney injury (AKI) but did not require dialysis. The patients renal function returned to their preoperative level prior to discharge. The patient died nine months later secondary to a sudden pulmonary embolism.

No patient in the fEVAR group suffered visceral artery occlusion though seven patients were noted to have compromise to a target visceral vessel (renal artery in six cases and SMA in one other). In five cases stenosis/angulation with abnormal waveforms of a renal artery was seen on arterial duplex but no secondary intervention was performed for the target vessel. In one case of stenosis of a renal artery with abnormal waveforms, the patient had a secondary intervention 8 months post-operatively to place a second renal stent, this corrected the abnormal flow within the renal artery. No patient required dialysis because of compromise to his or her renal artery. The other case of stenosis in a superior mesenteric artery was identified on duplex 8 years postoperatively in a patient who had a fenestration for each renal artery and a scallop for the SMA. No intervention was undertaken, and the patient remains alive and on the surveillance programme 11 years after the original operation without signs or symptoms of mesenteric ischaemia.

No visceral vessel occlusion was seen within the OR group; however, it should be noted that routine surveillance scanning did not take place in this group of patients and therefore it may be possible that occlusion could have occurred without being detected.

### **Renal Insufficiency and Need for Dialysis**

As stated above no patient required long-term dialysis throughout the follow up period, however one patient in the OR group did require temporary dialysis while an inpatient.

In determining acute renal dysfunction in the post-operative period, the Kidney Disease: Improving Global Outcomes (KDIGO) definition was used to define whether a patient suffered an acute kidney injury during their hospital stay. The KDIGO definition also has a staging system to enable severity of the acute kidney injury to be staged.

Regarding the post-operative in hospital period there was no significant difference in the maximum creatinine, the rate of AKI or the stage of AKI reached between the three groups (See table 9.10).

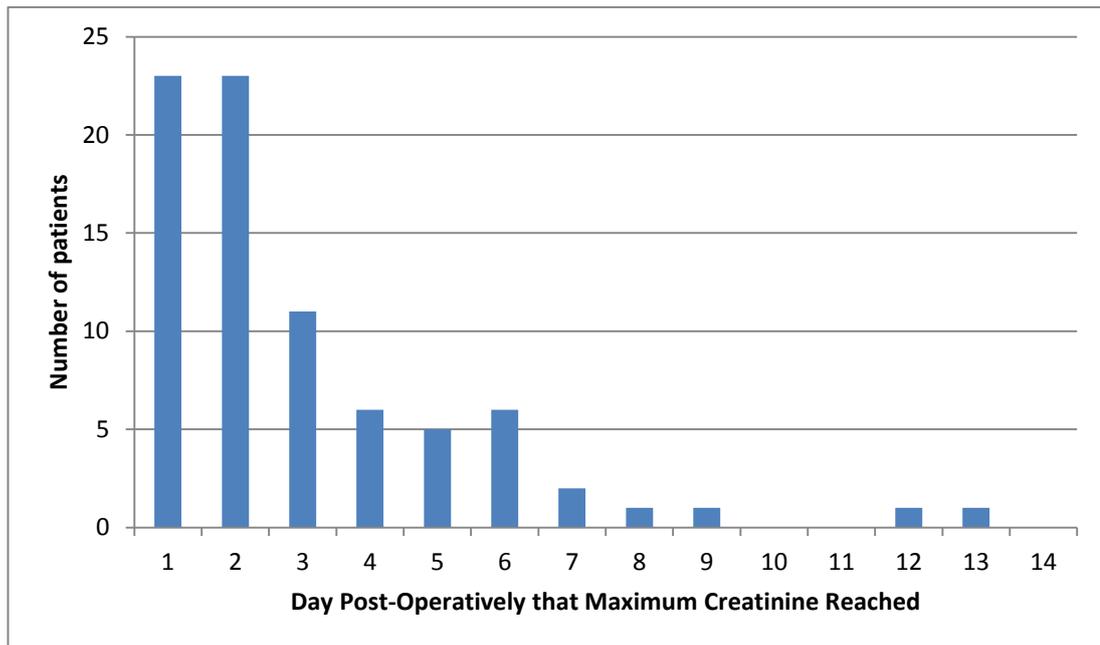
**Table 9.10 Renal Function Post Operatively.**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
<b>Max Cr post op (in-hospital), median (IQR)</b>	110 (94, 150)	110 (81, 145)	118 (84, 154)	115 (87, 151)	0.697
Missing data (%)	0 (0)	0 (0)	1 (2.7)	1 (1.3)	
<b>AKI post-op (In Hospital), n (%)</b>					0.258
No	21 (75.0)	12 (80.0)	20 (54.1)	53 (66.3)	
Yes	7 (25.0)	3 (20.0)	16 (43.2)	26 (32.5)	
Missing	0 (0)	0 (0)	1 (2.7)	1 (1.3)	
<b>AKI stage (In-Hospital), n (%)</b>					1.000
1	7 (25.0)	3 (20.0)	12 (32.4)	22 (27.5)	
2	1 (3.6)	0 (0)	3 (8.1)	4 (5.0)	
3	0 (0)	0 (0.0)	1 (2.7)	1 (1.3)	
No AKI	20 (71.4)	12 (80.0)	21 (56.8)	53 (66.3)	

Table 9.10 - Comparison of continuous variables was performed using one-way ANOVA when they were normally distributed and Kruskal-Wallis test (\*) when not.

During the in hospital stay the maximum creatinine for each patient was usually reached within 3 days of the operation (70% of patients). The median day for creatinine to peak for the whole cohort was day 2. (See figure 9.5)

*Figure 9.5 Time to Reach Maximum Post-Operative Creatinine.*



With regards to chronic kidney disease the KDIGO definition of an abnormality of kidney structure or function which is present for > 3 months was used. The eGFR was used to define whether a patient had chronic kidney disease or not pre-operatively and during follow up after their operation. Chronic kidney disease was graded and categorised according to the system recommended by KDIGO. Patients with an eGFR of >60 were considered not to have chronic kidney disease. The CKD category for given eGFR values is as follows: eGFR 45 – 59 (category G3a), eGFR 30 – 44 (category G3b), eGFR 15 – 29 (Category G4), eGFR <15 (Category G5). The use of these definitions for both acute kidney injury and chronic kidney disease are recommended by The Renal Association in the UK.

Over the remainder of follow up there were no significant differences in the renal function between the three groups as measured by the last eGFR recorded during follow up or whether any patient had a deterioration of renal function sufficient enough to change their grade of CKD. Deterioration of renal function in this regard was defined as the eGFR dropping sufficiently so that a patients CKD grading would be altered, i.e. from an eGFR of 61 to 59 would be classed as a deterioration in renal function, however it should be noted

that an eGFR dropping from 59 to 46 would not be classed (according to this definition) as a deterioration in renal function. (See table 9.11)

*Table 9.11 Renal Function during Follow up.*

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
Last eGFR during follow up(ml/min/1.73m <sup>2</sup> ), median (IQR)	43 (35, 54)	55 (49, 64)	54 (36, 71)	49 (37, 66)	0.120
Missing data (%)	2 (7.1)	2 (13.3)	9 (24.3)	13 (16.3)	
Change in eGFR (ml/min/1.73 m <sup>2</sup> ) (Last eGFR vs Pre-op eGFR), Median (IQR)	-10 (-22,-2)	-3 (-16,5)	-3 (-17,2)	-	0.228
Deterioration in renal function, n (%)					
No	12 (42.9)	11 (73.3)	19 (51.4)	42 (52.5)	0.057
Yes	14 (50.0)	2 (13.3)	9 (24.3)	25 (31.3)	
Missing	2 (7.1)	2 (13.3)	9 (24.3)	13 (16.3)	
Deterioration by 2 or more CKD grades, n (%)					
No	9 (32.1)	2 (13.3)	6 (16.2)	17 (21.3)	1.000

Yes	5 (17.9)	1 (6.7)	4 (10.8)	10 (12.5)	
No deterioration / Missing	14 (50.0)	12 (80.0)	27 (73.0)	53 (66.3)	

Table 9.11 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry. eGFR = Estimated Glomerular Filtration Rate, CKD – chronic kidney disease

As can be seen from the table there was no statistically significant difference in any of the variables measured, however those patients undergoing EVAR were, in this sample, more often exhibited a deterioration in their renal function as measured by CKD grades and change in eGFR. Of the fourteen patients that did have a deterioration in their renal function seven of them dropped their eGFR from >60 to 30 – 59. i.e. dropping from no chronic kidney disease to within stage 3a or 3b CKD. When comparing the last recorded eGFR during follow up with the preoperative value there was no statistically significant difference but the median eGFR change for EVAR patient was -10 compared with -3 for both other types.

#### **Reintervention Rates (In-hospital)**

No patients required an additional endovascular procedure while an inpatient however seven patients did return to theatre for an operative intervention while still an inpatient (See table 9.12).

**Table 9.12 Re-Interventions (In Hospital).**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
<b>Return to theatre (In hospital), n (%)</b>					0.288
<b>Yes</b>	4 (13.8)	0	3 (8.1)	7 (8.6)	
<b>No</b>	23 (82.8)	15 (100)	34 (91.9)	73 (90.1)	
<b>Unknown</b>	1 (3.4)	0	0	1 (1.2)	

Table 9.12 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry. eGFR = Estimated Glomerular Filtration Rate, CKD – chronic kidney disease

Four patients who initially underwent EVAR returned to theatre; three for incision and drainage of a groin haematoma and to ensure haemostasis was achieved (Day 0, 1 and 9). One further EVAR patient returned to theatre on the eighth post-operative day and underwent a laparotomy and over sewing of a gastric perforation.

Three patients required return to theatre after open repair:

- One patient was haemodynamically unstable and thought to be bleeding intraabdominally. They returned to theatre within the first post-operative day and bleeding from the aneurysm sac edge was found to be the cause for their instability. Haemostasis was subsequently achieved.
- Another patient suffered left leg ischaemia on day 1 post operatively and returned to theatre for thromboembolectomy and fasciotomy. This restored perfusion to that leg and the patient subsequently made a good recovery.
- The final patient underwent a prolonged operation (> 11 hours) with suprarenal clamp, there was an estimated 7000mls blood loss during the operation and post operatively the patient developed abdominal compartment syndrome and multiorgan failure. On day 2 post operatively, they returned to theatre for

abdominal decompression and placement of VAC dressing. They returned to theatre for numerous changes of abdominal VAC and required prolonged critical care stay. The patient was eventually discharged from the hospital and remains alive.

**Reintervention Rates (During Follow Up)**

There were 16 re-interventions in 12 patients during the follow up period, nine operative surgical interventions and seven radiological interventions. One patient in the EVAR group underwent 3 radiological re-interventions and two operative reinterventions for a groin lymphocele. The following table documents all the re-interventions performed during the follow up period (See table .7).

*Table 9.13 Re-intervention procedures During Follow Up*

<b>Repair Group</b>	<b>Re-intervention</b>	<b>Time from Initial Procedure</b>	<b>Outcome</b>
<b>EVAR</b>	Mesenteric angiogram	2 months	No abnormality detected
	USS guided lymphocele drainage <sup>a</sup>	5 months	Recurred
	USS guided lymphocele drainage and injection of alcohol <sup>a</sup>	6 months	Recurred
	I+D Groin Lymphocele <sup>a</sup>	7 months	Needed further debridement
	USS guided lymphocele drainage and injection of alcohol and tetracycline <sup>a</sup>	8 months	Needed surgical debridement
	Debridement of Groin Wound <sup>a</sup>	9 months	Prolonged convalescence but did fully heal
	Conversion to Open repair	13 months	Successful
	Conversion to Open Repair	13 months	Successful
	Conversion to Open Repair	37 months	Successful
	Proximal extension cuff and right renal stent (Migration)	66 months	Successful
	Limb extension and embolisation of IIA to extend seal (Aneurysm expansion)	96 months	Successful
<b>fEVAR</b>	Right renal stent – Scallop to renal artery initially but shuttering noted with damped waveform	8 months	Renal artery waveform normalised after procedure
	Femoro-femoral Crossover graft (Occlusion of limb of bifurcated portion of stent graft)	92 months	Successful

<b>Open Repair</b>	Femoro-femoral Crossover graft (Occlusion of limb of bifurcated graft)	2 months	Successful
	Anterior abdominal wall skin graft	3 months	Successful
	Incisional hernia repair (open)	33 months	Successful

Table 9.13 - I+D=Incision and drainage, USS=Ultrasound scan, IIA=Internal Iliac artery. a=Same patient underwent numerous separate interventions

The patient in the fEVAR group who underwent a fem-fem crossover 92 months after the index procedure was lost to follow up for a period of three years. Initially the patient had had 4 years of post-operative follow up with a standard protocol and no problems were identified. They were lost to follow up for 3 years then presented with an acutely ischaemic leg. CT angiogram on admission revealed an occluded limb but the rest of the fEVAR was patent with no issues. The patient underwent a successful femoro-femoral crossover graft but was found to have oesophageal cancer with metastatic disease and died 6 weeks later during the same admission. The only predisposing factor found to account for the thrombosed limb was the advanced malignancy. There was no significant difference found between the three groups for occurrence of surgical re-intervention, radiological re-intervention or 'any re-intervention' (See table 9.14).

**Table 9.14 Re-Interventions (Follow up)**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
<b>Patients who returned to Theatre (Long term), n (%)</b>					0.409
<b>No</b>	20 (71.4)	13 (86.7)	30 (81.1)	62 (77.5)	
<b>Yes</b>	4 (14.3)	1 (6.7)	3 (8.1)	9 (11.3)	
<b>Unknown</b>	4 (14.3)	1 (6.7)	4 (10.8)	9 (11.3)	
<b>Patients who returned to Radiology (Long term), n (%)</b>					0.027
<b>No</b>	20 (71.4)	13 (86.7)	33 ( 89.2)	66 (82.5)	
<b>Yes</b>	4 (14.3)	1 (6.7)	0 (0)	5 (6.3)	
<b>Unknown</b>	4 (14.3)	1 (6.7)	4 (10.8)	9 (11.3)	
<b>Any secondary intervention (Long term), n (%)</b>					0.167
<b>No</b>	17 (60.7)	12 (80.0)	30 (81.1)	59 (73.8)	
<b>Yes</b>	7 (25.0)	2 (13.3)	3 (8.1)	12 (15.0)	
<b>Unknown</b>	4 (14.3)	1 (6.7)	4 (10.8)	9 (11.3)	

Table 9.14 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry.

### **Conversion to Open Repair**

There were three cases of conversion to open repair, all within the EVAR group. No patient that underwent fEVAR underwent open conversion though this difference between EVAR and fEVAR did not reach statistical significance ( $p=0.541$ ).

The cases of conversion to open repair are described below:

- The first case was in a patient with an aneurysm that breached IFU on two counts; maximum neck diameter of 33mm, and presence of thrombus. An EVAR with a proximal body diameter of 36mm was implanted without complication. The patient made an excellent recovery and no complications were noted until at 36 months post-operatively significant migration was detected on surveillance scanning. The patient then underwent open conversion, recovered well and died of non-aneurysm related cause 113 months after the original EVAR.
- The second patient had an aneurysm that breached the IFU on five counts; neck length (5mm), conical, large diameter neck (34mm),  $\beta$  angle of  $61^\circ$  and presence of thrombus. An EVAR stent-graft with a proximal body of 30mm was implanted and the patient made a full, uncomplicated recovery. 12 months post-operatively the patient was found to have migration of the stent-graft with only a short seal zone remaining. Conversion to open repair was undertaken at 13 months. 42 months post-operatively the patient died from an unknown cause.
- The third patient had an aneurysm that breached the IFU on two counts; maximum neck diameter (38mm) and  $\alpha$  angle of  $47^\circ$ . The EVAR was implanted successfully but a type 1a endoleak was noted at the end of the procedure. This was managed conservatively but one year post-operatively the endoleak was still present and migration was noted to have occurred. Conversion to open repair was therefore undertaken at 13 months. The patient recovered well with no further aneurysm

related problems through follow up. The patient died of an unknown cause 127 months after the original EVAR.

**Major Complications (In hospital)**

There was a variety of post-operative complications recorded. Complications were classified according to published reporting standards[93]. This system of classification first recognises three groups or types of complication; deployment related complications, implant related complications and systemic complications. Implant related complications include features such as stent-graft migration and for the most part include complications that tend to only occur or be detected within the surveillance programme, after discharge from hospital. As such, there were no implant related complications within any of the three groups during their primary hospital stay. Within each group complications are then assigned a degree of severity; mild, moderate or severe. A mild complication indicates that the complication has occurred but resolved spontaneously without prolonging hospital stay or causing permanent impairment. A moderate complication indicates the need for significant intervention, prolongation of hospital stay and/or permanent disability, which does not preclude normal daily activity. A severe complication indicates the need for major surgical or medical intervention, which may be accompanied by prolonged convalescence, permanent disability and may result in death. There were 79 post-operative complications in 51 patients. The table below details these complications (See Table 9.15).

*Table 9.15 Post-Operative Complications (In hospital)*

Type of Repair	Complication Group	Complication	Complication severity	Number of complications
EVAR	<i>Deployment Related</i>	Access site	Mild	2
		Haematoma	Moderate	3
		Groin Lymphocele	Mild	1
		Operative Blood Transfusion	Moderate	1
		Peripheral Embolisation	Severe	1
	<i>Systemic Complications</i>	Gastrointestinal	Severe	2
		Pulmonary	Mild	3
		Renal Insufficiency	Mild	1
Urological		Mild	1	
fEVAR	<i>Deployment Related</i>	Access site	Mild	1
		Haematoma	Mild	1
		Operative Blood Transfusion	Moderate	1
	<i>Systemic Complications</i>	Cardiac	Mild	2
		Pulmonary	Mild	3
		Renal Insufficiency	Mild	1
		Urological	Mild	2
Open Repair	<i>Deployment Related</i>	Operative Blood transfusion	Mild	9
			Moderate	14
			Severe	2
		Peripheral Embolisation	Mild	1
		Peripheral Ischaemia	Moderate	1
	<i>Systemic Complications</i>	Abdominal compartment	Severe	1

		syndrome		
		Cardiac	Mild	6
			Moderate	4
			Severe	1
		Cerebrovascular	Moderate	2
		Coagulopathy	Severe	1
		Gastrointestinal	Mild	1
			Moderate	2
		Pulmonary	Mild	3
			Moderate	3
			Severe	1
		Renal	Moderate	1
		Urological	Mild	1

In line with the reporting standards [93] intraoperative blood transfusion is graded as a complication. If a patient receives < 2 units of autologous transfusion with no homologous transfusion it is considered a mild complication. If the patient receives >2 units autologous but < 3 units homologous then it is a moderate complication and if >3 units homologous blood transfusion, then it is a severe complication. Of note, in the open operation group there were 14 moderate and 2 severe complications related to intraoperative blood transfusion. This is in line with the reporting standards however; it should be borne in mind these reporting standards were developed primarily with endovascular repair in mind. As such, what would be considered an unusual and excessive intraoperative blood transfusion when carrying out endovascular repair may be considered routine and even 'normal' for an open operation.

An analysis of major complications between the three repair groups was undertaken including the definition of major complication from the reporting standards and applying it equally to all three groups. A complication was considered major if it fell into either the moderate or severe categories or minor if it fell into the mild category. There was a no statistically significant difference found between the three groups when comparing major complications as defined in the reporting standards. An analysis was also conducted excluding moderate intraoperative blood transfusion from the definition of major complication and only including severe. This analysis also revealed no statistically significant difference in the incidence of major complications between the three groups. (See table 9.16).

**Table 9.16 Patients Experiencing Major Complications (In-Hospital)**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
<b>Major Complications<sup>a</sup> (In hospital), n (%)</b>					0.494
No	24 (85.7)	14 (93.3)	17 (45.9)	55 (68.8)	
Yes	4 (14.3)	1 (6.7)	20 (54.1)	25 (31.3)	
<b>Major Complications<sup>b</sup> (In hospital), n (%)</b>					0.101
No	24 (85.7)	15 (100)	26 (70.3)	65 (81.3)	
Yes	4 (14.3)	0 (0)	11 (29.7)	15 (18.7)	

Table 9.16 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry.

. a = Major complications including moderate intraoperative blood loss as major complication. b=Excluding moderate blood loss as a major complication.

During the mid to long term follow up a further nine patients suffered nine complications related to their initial operation, not including issues related to stent-grafts (these are discussed separately). (See table 9.17)

**Table 9.17 Complications not Relating to the Stent-Graft (During Follow Up)**

<b>Repair Type</b>	<b>Complication</b>	<b>Intervention</b>
<b>EVAR</b>	Groin Lymphocele	Incision and drainage
<b>EVAR</b>	Abdominal pain -? Mesenteric ischaemia	Mesenteric angiogram – No vascular cause found
<b>Open Repair</b>	Retrograde Ejaculation	No intervention
<b>Open Repair</b>	Infected Aortic Graft (5 years) – Source: empyema of the gallbladder	Long term antibiotics
<b>Open Repair</b>	Right limb occlusion (2 months)	Femoral-femoro crossover
<b>Open Repair</b>	Incisional hernia (12 months)	Operative repair
<b>Open Repair</b>	Incisional hernia	Conservative management
<b>Open Repair</b>	Incisional hernia	Conservative management
<b>Open Repair</b>	Buttock Claudication	Conservative management

#### 9.4.4. Aneurysm Morphology

Pre-operative CT scans were reviewed for all patients and various anatomical data were collected for each patient. The following table summarises these data. (See table 9.18)

**Table 9.18 Aneurysm Morphology**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
Max Aneurysm Diameter (mm), Median (IQR)	66.5 (60.5,70.0)	60.0 (57.0,64.0)	65.0 (60.0,77.5)	64.0 (59.0,70.0)	0.018
Neck Length (mm), Median (IQR)	20.0 (15.0,23.5)	4.0 (0.0, 9.0)	6.0 (1.5,14.5)	10.0 (4.0,18.0)	<b>&lt;0.001</b>
Neck Diameter (mm), Median (IQR)	28.0 (25.5,30.0)	34.0 (31.0,40.0)	35.0 (28.5,42.5)	31.0 (28.0,38.0)	0.001
$\alpha$ angle ( $^{\circ}$ ), Median (IQR)	25.0 (8.0,40.5)	16.0 (14.0,24.0)	36.0 (16.5,57.0)	25.5 (13.0,43.0)	0.026
$\beta$ angle ( $^{\circ}$ ), Median (IQR)	40.0 (29.5,58.5)	37.0 (20.0,45.0)	45.5 (26.5,67.5)	41.0 (27.0,60.0)	0.229
Thrombus, n (%)					0.397
No	14 (50.0)	10 (66.7)	23 (62.2)	47 (58.8)	
Yes	14 (50.0)	4 (26.7)	13 (35.1)	31 (38.8)	
Unknown	0 (0)	1 (6.7)	1 (2.7)	2 (2.5)	
Calcification, n (%)					0.827
None	8 (28.6)	4 (26.7)	15 (40.5)	27 (33.8)	
Mild	13 (46.4)	6 (40.0)	15 (40.5)	34 (42.5)	
Moderate	6 (21.4)	3 (20.0)	4 (10.8)	13 (16.3)	
Severe	1 (3.6)	1 (6.7)	2 (5.4)	4 (5.0)	

Unknown	0 (0)	1 (6.7)	1 (2.7)	2 (2.5)	
<b>Number of IFU violations, n (%)</b>					
1	12 (42.9)	1 (6.7)	6 (16.2)	19 (23.5)	
2	11 (39.3)	4 (26.7)	8 (21.6)	23 (28.4)	
3	4 (14.3)	8 (53.3)	10 (27)	23 (28.4)	
4	0	2 (13.3)	9 (24.3)	11 (13.6)	
5	1 (3.6)	0	3 (8.1)	4 (4.9)	
Unknown	0	0	1 (2.7)	1 (1.2)	
<b>Number of IFU violations, median (IQR)</b>	2.0 (1.0, 2.0)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	2.0 (2.0, 3.0)	0.001
<b>Expected clamp site, n (%)</b>					0.061
Infrarenal	24 (85.7)	9 (60.0)	22 (59.5)	55 (68.8)	
Suprarenal	0 (0)	2 (13.3)	7 (18.9)	9 (11.3)	
Supracoeliac	4 (14.3)	4 (26.7)	8 (21.6)	16 (20.0)	

Table 9.18 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry.

All aneurysms were noted to be atherosclerotic in nature with the vast majority having a fusiform shape. Only four patients had an aneurysm with a non-fusiform shape. In each case, the shape would best be described as dumb-bell. The smallest aneurysm in the series was 55mm in maximal diameter and the largest was 110mm. The median aneurysm diameter was 64mm. Although not statistically significantly different those patients who underwent fEVAR had a smaller median aneurysm diameter of 60mm, compared with 66.5mm for EVAR patients and 65mm for open repair patients.

The neck length was significantly longer in patients who received standard EVAR. Only six patients (21.4%) in the EVAR group had a neck length outside the IFU, with the minimum

length treated being 5mm. This is perhaps unsurprising given the fact that neck length is one of the primary areas of scrutiny when deciding what type of repair a patient should have.

There was no statistically significant difference between the groups when comparing neck diameter although there was a trend towards a smaller neck diameter in the EVAR group (28mm) when compared with the other two groups - open repair (35mm) and fEVAR (34mm). In fact, the median neck diameter in this group is within the IFU for standard EVAR ( $\leq 32$ mm) but larger in the other two groups.

Again, there was no statistically significant difference between the groups in terms of median  $\alpha$  or  $\beta$  angle. Though there was a trend towards a smaller alpha angle in fEVAR patients. The alpha angle represents angulation within the visceral segment of the aorta between the SMA and the beginning of the aneurysm below. This is precisely the segment where EVAR and fEVAR are placed to achieve a 'seal'. Furthermore, in fEVAR, the fact that the device requires careful manipulation and placement to align the visceral vessels with the precisely manufactured fenestrations mean that angulation would be less well tolerated as it would distort the anatomy and make accurate placement of the device very difficult. In open repair, there are no such concerns and hence may be why patients with a significantly larger  $\alpha$  angle were preferentially treated with open repair.

There was no statistically significant difference found between the groups when comparing presence of thrombus or degree of calcification within the neck. In fact, when calcification was considered to be simply either present or not there was still no significant difference between the groups. This suggests that distribution of calcification was relatively homogenous between the three groups and did not significantly affect whether a patient had one type of operation or another. With regards to calcification, the IFU for the three standard stent-grafts that were consulted during the design of the study differ in their

consideration of calcification and whether its presence constitutes a breach of the IFU. In two cases, the IFU simply states that if 'significant' calcification is present then the aneurysm would be outside IFU. For the third device presence of calcification at 'implantation sites' is considered to represent a breach of the IFU. There is no standard agreed definition as to what constitutes significant calcification. The presence of calcification and its degree were determined subjectively during the data collection. For these reasons the presence of calcification was not considered to represent an IFU violation and therefore further analysis took this into account. In no patient was presence of calcification the sole breach of IFU and therefore the sole reason for inclusion into the study.

The median number of IFU violations for each of the groups approached but did not reach statistical significance. EVAR patients had a median of 2 IFU violations per patient and fEVAR and OR patients had 3. This is perhaps unsurprising given that standard EVAR is by definition not intended for use in patients with any IFU violation and is less likely to be the treatment choice selected when there are multiple factors violating its intended use. fEVAR on the other hand is specifically designed to be used in patients who exhibit violations to standard EVAR IFU. Furthermore, open repair is not limited by the same anatomical constraints and therefore in an era when most patients receive an endovascular solution to treat their aneurysm if suitable, the majority of the remaining patients who receive open repair will exhibit a higher preponderance for IFU violations. The most common reason for IFU violation in all three groups was conicality of the neck: 63 patients (78.8%). The Reasons for IFU violations are explored in the table below (See table 9.19):

**Table 9.19 IFU Violations**

IFU Violation	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)
Neck Length, n (%)	6 (21.4)	13 (86.7)	22 (59.5)	42 (52.5)
Neck Diameter, n (%)	5 (17.9)	9 (60)	20 (54.1)	35 (43.8)
Conicality, n (%)	18 (64.3)	14 (93.3)	31 (83.8)	63 (78.8)
α angle, n (%)	4 (14.3)	0	11 (29.7)	15 (18.8)
β angle, n (%)	6 (21.4)	1 (6.7)	9 (24.3)	16 (20)
Significant Thrombus, n (%)	12 (42.9)	4 (26.7)	10 (27)	27 (33.8)

Table 9.19 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher’s exact test or χ<sup>2</sup> test, depending on the amount of data present in each entry. IFU=Instructions for use. The number represents the number of patients that exhibited that feature outside of IFU. As patients can exhibit more than one IFU violation the percentages add up to more than 100%.

Expected clamp site, as judged from the pre-operative CT scan, did not differ significantly between the three groups. The only group in which an actual clamp was placed is that of the open repair group. The following table shows the distribution of predicted clamp site with actual clamp site in the open repair group (See table 9.20)

**Table 9.20 Expected Versus Actual Clamp Site**

Expected Clamp Site, n	Actual Clamp Site, n		
	Infrarenal	Suprarenal	Supracoeliac
Infrarenal	<b>15 (75%)</b>	4 (20%)	1 (5%)
Suprarenal	3 (60%)	<b>2 (40%)</b>	0
Supracoeliac	3 (50%)	3 (50%)	<b>0</b>

In this cohort of patients if an Infrarenal clamp was predicted from the pre-operative CT scan, 75% of the time an infrarenal clamp was placed. However, when suprarenal or

supraceliac clamp was predicted <20% of the time that clamp was placed intraoperative. Fisher's exact test was applied in order to investigate the association of expected and actual clamp site in open repair patients. The results suggested that there is not a statistically significant relationship between the variables mentioned above ( $p=0.636$ ).

#### **9.4.5. Operative data**

All patients underwent their procedure in the operating theatre under general anaesthetic. No patient died intraoperative and there were no immediate conversions to open repair in the endovascular group. For those that received endovascular repair the device was placed under fluoroscopic guidance using a mobile C-arm in theatre. There was a radiologist present in theatre (along with a surgeon) for all the fEVAR cases, all but five of the EVAR cases and none of the OR cases.

The following table details information relating to intraoperative variables. (See table 9.21)

**Table 9.21 Intraoperative Data**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
Operation time (mins), Median (IQR)	210 ( 165, 240 )	315 ( 270, 360 )	240 ( 173, 300 )	240 ( 180, 300 )	0.001
Estimated blood loss (ml), median (IQR)	800 ( 800, 800 )	1000 (1000,2000 )	1650 ( 950,2000 )	1250 ( 800,2000 )	0.314
Missing data (%)	23 ( 82.1% )	12 ( 80.0% )	17 ( 45.9% )	52 ( 65.0% )	
Intraoperative Transfusion (mls), Median (IQR)	0 (0, 0 )	0 (0, 250 )	500 ( 255, 800 )	0 (0, 500 )	<b>&lt;0.001</b>
Persistent Intraoperative Graft related Endoleak (Type I or III), n (%)					0.290
Yes	4 (14.3)	2 (13.3)			
No	24 (85.7)	13 (86.7)			

Table 9.21 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher’s exact test or  $\chi^2$  test, depending on the amount of data present in each entry.

The operation time was longer with fEVAR compared with either open repair or EVAR, which given the increased complexity of the procedure necessitating multiple vessel cannulation and stenting is unsurprising, yet this failed to reach statistical significance. Again, somewhat unsurprising is that the estimated blood loss and volume of intraoperative blood transfusion is greater in open repair.

There were four cases of persistent intraoperative graft related endoleak (all type 1a) noted on completion angiogram in the EVAR group. In all cases a moulding balloon was used at the proximal attachment site which reduced the endoleak but did not abolish it. In each case it was decided to manage the endoleak expectantly with close surveillance on follow up as it was felt that the endoleaks were small and of low flow and would therefore seal spontaneously. The outcome for each patient is described above in the section on technical success and is repeated here for clarity. Of the four cases of persistent type 1a endoleak: One patient had no further type 1a endoleak identified during the follow up and died approximately nine years postoperatively from non-aneurysm related cause. Three patients had a type 1a endoleak identified at some point during the follow up:

- One was only seen on the one-month surveillance scan and never again, patient died of unknown cause nearly five years after the original operation.
- One patient had migration and further type 1a endoleak identified and successfully underwent a conversion to open repair within the first year after their index operation. The patient recovered well and remained alive for approximately 10 years until their death of unknown cause.
- The final patient had migration and type 1a endoleak noted but died from a ruptured aneurysm prior to conversion to open repair.

There were two cases of graft related endoleak (both type 3) within the fEVAR group. They were both arising from the junction between the main fenestrated stent graft body and a renal artery stent. In both cases the renal stent was “re-locked” with an angioplasty balloon but the endoleak persisted. In both cases the endoleak was never seen on surveillance imaging during follow up. There was no significant difference seen in the proportion of patients undergoing unplanned adjunctive manoeuvres between the EVAR and fEVAR groups. The adjunctive manoeuvres performed were as follows: In the EVAR group;

- Iliac limb stenting/angioplasty (Five patients)
- Moulding balloon use at top end (two patients)
- Placement of a zenith cuff for type 1 endoleak (one patient)
- Placement of Palmaz stent for type 1 endoleak (one patient)

In the fEVAR group;

- Extra TV stent due to maldeployment of first (two patients)
- Balloon moulding of TV stent connection due to endoleak (two patients)
- Iliac limb angioplasty (one patient)

In the majority of patients undergoing a repair by endovascular means, the incision used was bilateral oblique groin incisions to gain access to the femoral arteries for subsequent cannulation. In two patients undergoing EVAR a different incision was used: in one patient in whom there was contralateral iliac occlusion and significant ipsilateral disease a Rutherford Morrison incision was used, and an ilio-femoral bypass procedure was performed to act as a conduit for deployment of an aorto-uni-iliac device. In the other case the patient had short common iliac arteries and standard endovascular repair would necessitate coverage of both internal iliac ostia. Instead, on one side a Rutherford Morrison incision was used to gain access and then a surgical internal iliac artery transposition to the distal external iliac artery was performed. This allowed deployment of the stent graft into both external iliac arteries while maintaining internal iliac perfusion from one side. All cases of fenestrated EVAR utilised bilateral oblique groin incisions only for access. In the OR group only two patients did not have a midline laparotomy incision. In each case, they had a rooftop incision to gain access.

One case utilised a surgical conduit for deployment of the endovascular stent-graft. This was planned beforehand and is described above. There were no cases of conversion to open repair within either endovascular group at the primary operation.

There were six immediate complications after the primary operation, three in the EVAR group and three in the OR group. No immediate complications were seen in the fEVAR group; however, this difference did not reach statistical significance (p=0.651). The complications are detailed below (see table 9.22)

**Table 9.22 Immediate Complications**

Type of Repair	Complication	Action
<b>EVAR</b>	Bleeding from left groin – In recovery	Taken to theatre and haemostasis achieved
<b>EVAR</b>	Inadvertent renal artery coverage	Attempts to recanalise in theatre, unsuccessful.
<b>EVAR</b>	Cholesterol embolization left leg	Managed on critical care unit with inotropic support
<b>Open</b>	Ischaemic leg	Taken to theatre for popliteal embolectomy
<b>Open</b>	Bleeding intraabdominally	Taken to theatre and haemostasis achieved
<b>Open</b>	No left femoral pulse	Aortofemoral bypass undertaken immediately

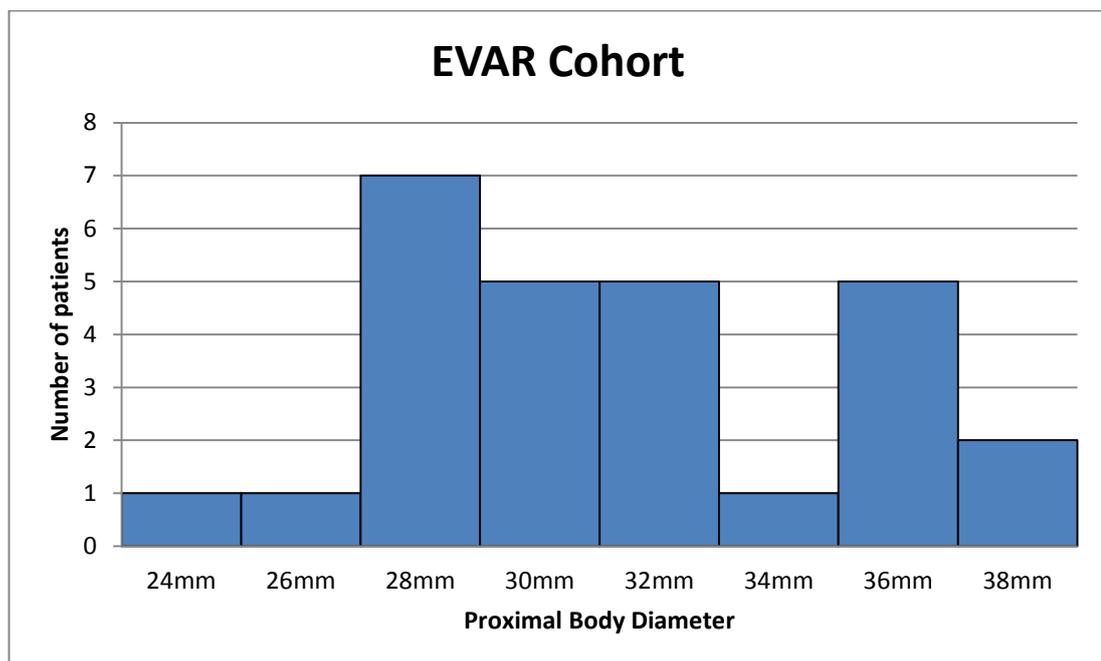
#### **9.4.6. Stent Graft configuration**

In all cases of fenestrated EVAR the Zenith Fenestrated (Cook Inc. Bloomington, Indiana) platform was used. In the EVAR group all 28 patients received a stent-graft from the Zenith Flex (Cook Inc. Bloomington, Indiana) platform. One patient within the EVAR group received a custom-made Cook device that did not have suprarenal fixation as part of the implanted stent graft system. All the remaining patients treated by endovascular means

had suprarenal fixation. In all cases of fEVAR the distal main body was bifurcated. Regarding standard EVAR all but one were bifurcated main bodies. One case of aorto-uni-iliac device was described earlier.

The following graph presents the diameters of the proximal main body portion for all standard endovascular device utilised: (See Figure 9.6)

*Figure 9.6 Proximal Body Diameter in EVAR Cohort*



The following table documents stent-graft configuration with relation to target vessels for the fEVAR cohort (See table 9.23)

*Table 9.23 Stent-Graft Configuration for fEVAR*

Number of Target vessels	Configuration	Number of patients
4	Sc CA/SMA (Conjoined origin), Fen LRA/RRA	1
3	Fen SMA/LRA/RRA	3
	Sc SMA, Fen RRA/LRA	9
	Sc SMA/RRA, Fen LRA	1
2	Fen RRA, Sc LRA	1

There were 45 target vessels in total, mean of 3 target vessels per patient (Standard deviation 0.38). Fourteen target vessels were protected with a scallop, two with a large fenestration and 29 with small fenestrations. No target vessels protected with a scallop and one target vessel protected by a large fenestration received a stent. All target vessels protected with a small fenestration and one by a large fenestration, however, were stented. In total 31 target vessel stents were placed in 30 target vessels. One target vessel received two stents due to inadvertent distal deployment of the first stent. A second stent was required to complete the stenting and achieve a seal. Bare metal stents were used in 15 target vessels (Palmaz Genesis, Cordis Corp.) and covered stents were used in the other fifteen (Advanta, Atrium Medical.). In four patients, a mix of stent types were used.

#### 9.4.7. Post-operative data

There was a significant difference in length of stay both in a critical care environment post-operatively and overall hospital stay between the three groups. The following table details the length of stay for the three groups (See Table 9.24)

**Table 9.24 Length of Stay**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)	P - value
Critical care stay (days), Median (IQR)	0 (0, 0)	0 (0, 0)	1 (0, 2)	0 (0, 1)	<b>&lt;0.001</b>
LOS (days), Median (IQR)	7 (5, 9)	5 (4, 8)	13 (8, 20)	8 (6, 14)	<b>&lt;0.001</b>

Table 9.24 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry. LOS=Length of stay.

When comparing complications specific to the endovascular technique, namely, conversion to open repair, presence of endoleak during follow up, aneurysm expansion, or migration, only migration revealed a statistically significant difference in the occurrence of migration at any point during the follow up. (See table 9.25)

*Table 9.25 Complications Specific to the Endovascular Technique during Follow Up*

Variable	EVAR (n=28)	fEVAR (n=15)	Total (n=43)	P - value
<b>Open Conversion, n (%)</b>				0.541
No	25 (89.3)	15 (100.0)	40 (93)	
Yes	3 (10.7)	0 (0)	3 (7)	
<b>Endoleak (Any), n (%)</b>				0.734
No	17 (60.7)	10 (66.7)	27 (62.8)	
Yes	10 (35.7)	4 (26.7)	14 (32.6)	
Unknown	1 (3.6)	1 (6.7)	2 (4.7)	
<b>Endoleak (Graft Related), n (%)</b>				0.539
No	24 (85.7)	14 (93.3)	38 (88.4)	
Yes	3 (10.7)	0 (0)	3 (7)	
Unknown	1 (3.6)	1 (6.7)	2 (4.7)	
<b>Aneurysm Expansion (≥5mm), n (%)</b>				0.539
No	24 (85.7)	14 (93.3)	38 (88.4)	
Yes	3 (10.7)	1 (6.7)	4 (9.3)	
Unknown	1 (3.6)	0 (0)	1 (2.3)	
<b>Migration (≥ 5mm), n (%)</b>				
No	18 (64.3)	14 (93.3)		<b>0.017</b>
Yes	9 (32.1)	0 (0)		
Unknown	1 (3.6)	1 (6.7)		

Table 9.25 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry. LOS=Length of stay.

The prevalence of type 2 endoleak during follow up for both EVAR and fEVAR groups was similar with no statistically significant difference identified. There were seven cases (25%)

within the EVAR group of type 2 endoleak noted during follow up. There were four cases (26.7%) of type 2 endoleak within the fEVAR group. No patient underwent a secondary intervention associated with their type 2 endoleak and two patients, one within the EVAR group and one within the fEVAR group, who had a type 2 endoleak noted during follow up had aneurysm expansion of  $\geq 5$ mm. The EVAR patient had a type 2 endoleak noted on the first post-operative surveillance scan but it was never identified again on routine surveillance. Seven years after initial repair the patient was noted to have an increase in their aneurysm size of 5mm (from 39mm to 45mm maximal aneurysm diameter), there was tenuous seal within the common iliac artery at that point and the patient underwent an internal iliac artery embolization and stent graft extension into the external iliac artery. This procedure was done 92 months after the original EVAR and went without complication. The patient died 18 months later from non-aneurysm related cause. The fEVAR patient with a type 2 endoleak and expanding aneurysm had uneventful primary 3 vessel fEVAR and follow up until at 86 months follow up a type 2 endoleak was noted on surveillance and an aneurysm growth from 47 – 53mm. No intervention was undertaken, and the patient remains alive on the surveillance programme with an aneurysm that is 59mm on the most recent surveillance scan with no endoleak identified more than 11 years after the original operation.

#### **9.4.8 Comparison of Observed versus Expected In-hospital Mortality**

The British Aneurysm Repair (BAR) Score is a published, validated model that provides an estimate of the risk of in-hospital mortality, expressed as a percentage, for patients undergoing elective aneurysm repair. The BAR score was used to compare the observed deaths with those that would be expected according to this model.

In the cohort of 80 patients there was at least one data point missing relating to the BAR score in nine patients. Four patients were in the EVAR cohort and in all cases there was no record of a pre-operative ECG, therefore in-line with BAR methodology these patients had

a score of '0' given for the ECG component of the BAR calculation. The other five patients were in the OR group. Data missing in these cases included lack of information pertaining to previous cardiac history, no pre-operative ECG available and ASA grade. For all patients undergoing OR the mode of ASA was 2 and this was therefore used to calculate the BAR score for the four patients in which this data was missing.

The following table details the comparison of observed versus expected mortality for the patients using the BAR score calculated according to the type of repair they had. (See table 9.26)

**Table 9.26 Comparison of Observed Versus Expected Mortality using the BAR Score**

Variable	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Total (n=80)
Mean BAR score (%)	1.70	1.15	5.42	3.32
Expected number of deaths	0.48	0.17	2.00	2.66
Observed number of deaths	2	0	2	4
p-value	0.03	0.68	1.00	0.41

Table 9.26 - Comparison of categorical variables was performed using  $\chi^2$  test.

For patients undergoing fEVAR or OR there was no statistically significant difference between the number of observed deaths in each group compared with the expected number as predicted by their BAR score. However, for patients that underwent EVAR more patients died than would have been expected according to their BAR score, this result was statistically significant. This is interesting, and it could represent that compared with what was expected of these patients (if they had standard anatomy) but everything else was equal a validated risk prediction model predicted 0.5 deaths for the EVAR cohort, but 2 people actually died. With the only change from the data points inputted to the model

being that it was a non-standard aneurysm it may suggest that the anatomy play a part in the 'increased' mortality rate.

The following table details the comparison of observed versus expected mortality when the BAR score was calculated using the opposite type of repair (i.e. those who underwent EVAR or fEVAR; had their BAR score calculated as if they underwent OR) (See table 9.27)

*Table 9.27 Comparison of Observed Versus Expected Mortality for the Opposite Type of Repair using the BAR Score*

Variable	EVAR (n=29)	fEVAR (n=15)	Open Repair (n=37)	Total (n=81)
Mean BAR score (%)	8.01	5.61	1.14	4.38
Expected number of deaths	2.24	0.84	0.42	3.5
Observed number of deaths	2	0	2	4
p-value	0.87	0.32	0.01	0.79

Table 9.27 - Comparison of categorical variables was performed using  $\chi^2$  test.

For patients undergoing fEVAR or EVAR there was no statistically significant difference between the number of observed deaths in each group compared with the expected number as predicted by their BAR score (calculated as if they had undergone OR). However, for patients that underwent OR, more patients died than would have been expected according to their BAR score (calculated as if they underwent EVAR) this result was statistically significant.

#### 9.4.8. Risk Prediction Models

To try to develop a risk prediction model from the data gathered univariate modelling for the whole cohort was undertaken first, then for each repair group separately.

##### **Cox proportional hazards model (all cohort)- Univariate**

The tables below detail the results from fitting univariate Cox proportional hazards models to assess the relationship of different variables to survival over the follow up period. The different variables assessed were; age at operation, neck length, and expected clamp site. Proportional hazards assumption was checked and not violated in any of the cases below. The following table reports the outcome from fitting the Cox model for age and neck length (See table 9.28)

***Table 9.28 Relationship of Age and Neck Length with Survival Time Using Cox Proportional Hazards Model***

Variable	Hazard Ratio	95% Confidence Interval	p-value
Age	1.03	[0.99 – 1.06]	0.11
Neck Length (>15mm vs <15mm)	1.17	[0.69 – 1.97]	0.56

More specifically, For every one-year increase in a patient's age at operation, the hazard of dying is increased by 3%, although with 95% assurance this estimate could be between a 1% decrease to a 6% increase. The result failed to reach statistical significance. Regarding neck length patients were split into two groups ( $\geq 15$ mm or  $< 15$ mm). Patients with  $\geq 15$ mm neck length have almost a 17% increase in dying when compared to patients with smaller neck length, although with 95% assurance this estimate could be between 31% decrease to 97% increase. The result was not statistically significant.

The Cox model was also fitted for expected clamp site (Suprarenal vs Infrarenal and Supracoeliac vs Infrarenal separately) this again gave no statistically significant results with wide confidence intervals in each case (p-values of 0.68 and 0.75 respectively). The hazard

ratio comparing Suprarenal vs Infrarenal expected clamp was 0.82 with 95% confidence interval between 0.32 and 2.09. This suggests that patients with an expected suprarenal clamp may be expected to have between a 68% decrease in the event and 2.09 times higher chance of the event. This is statistically insignificant at the 0.05 level. Similarly, for the comparison between Supracoeliac and Infrarenal expected clamp the hazard ratio was 1.12 with a 95% confidence interval between 0.56 and 2.26. This was again not significant.

**Cox proportional hazards model (for each type of repair separately) - Univariate**

Cox proportional hazards models were also generated for each type of repair separately. Regarding neck length, it was not possible to split patients into two groups ( $\geq 15\text{mm}$  or  $< 15\text{mm}$ ), due to the low number of deaths observed. (see table 9.29)

*Table 9.29 Relationship of Age and Neck Length with Survival Time Using Cox Proportional Hazards Model for Each Type of Repair Separately*

Variable	Hazard Ratio	95% Confidence Interval	p-value
Age – EVAR	1.01	[0.96 – 1.07]	0.664
Age – fEVAR	1.03	[0.96 – 1.12]	0.377
Age – OR	1.02	[0.96 – 1.08]	0.470
Neck Length - EVAR	1.03	[0.98 – 1.09]	0.297
Neck Length - fEVAR	0.93	[0.80 – 1.08]	0.340
Neck Length - OR	1.008	[0.95 – 1.07]	0.806

As can be seen from the table there were no statistically significant results. The association of ASA grade (4 levels) and expected clamp site (3 levels) with survival was not possible to be investigated for those two groups separately, once more due to the low number of events observed.

Secondary analyses were also undertaken to determine the association between the factors above (age, neck length, ASA grade and expected clamp site) and whether a patient

achieved primary technical success and/or clinical success. For age at operation an independent samples t-test was used to compare the means of the normally distributed dependent variable (age) between the two primary technical success groups and separately between the two clinical success groups. Neither analysis reached statistical significance ( $p=0.247$  for technical success and  $0.0687$  for clinical success). This suggests no association between age and whether the patients' operation was primarily technical successful or not and whether it was clinically successful over the course of the entire follow up or not.

In order to investigate the association of neck length ( $\geq 15\text{mm}$  or  $< 15\text{mm}$ ), ASA grade and expected clamp site, Fisher's exact tests were generated. The results suggested that there is no statistically significant relationship between neck length ( $p = 1.000$ ), ASA grade ( $p = 0.454$ ), expected clamp site ( $p = 0.190$ ) and primary technical success. The same being true for clinical success with no statistically significant relationship for neck length ( $p = 0.069$ ), ASA grade ( $p = 0.066$ ), or expected clamp site ( $p = 0.433$ ).

The plan was then to undertake multivariate modelling in order to develop a robust and valid risk prediction model that could be applied to patients with non-standard aneurysms. However, the "rule of thumb" for Cox modelling suggests that a minimum of 10 outcome events (deaths in this case) per predictor variable should be present, therefore due to the low number of deaths observed it was not possible to generate multivariate models that would be valid or accurate.

#### **Alpha and Beta Angulation**

In order to investigate the role of angulation further logistic regression modelling was undertaken to determine if alpha or beta angulation played any statistically significant role in various outcome measures. The influence of angulation was first assessed with regards to primary technical success, in hospital mortality and reintervention within 30 days for the whole cohort. (see table 9.30)

*Table 9.30 - Univariate logistic model - Perioperative*

Outcome Measure	Characteristic	Odd's Ratio (95% confidence interval)	P-value
Primary Technical Success	$\alpha$ angulation	0.990 (0.962,1.018)	0.466
	$\beta$ angulation	0.992 (0.959,1.027)	0.653
Reintervention (<30 days)	$\alpha$ angulation	0.980 (0.939,1.022)	0.340
	$\beta$ angulation	1.007 (0.969,1.046)	0.736
In hospital mortality	$\alpha$ angulation	1.012 (0.973,1.052)	0.549
	$\beta$ angulation	1.007 (0.958,1.057)	0.794

For the outcomes; primary technical success, reintervention within 30 days and in hospital mortality the variable  $\alpha$  angulation and  $\beta$  angulation have no statistical significance at the 2.5% level (the significance level has been adjusted by Bonferroni). Next the influence of angulation with regards to clinical failure, reintervention over the longer term and mortality through follow up was assessed (see table 8.29)

*Table 9.31 - Univariate logistic model - During Follow up*

Outcome Measure	Characteristic	Odd's Ratio (95% confidence interval)	P-value
Clinical Failure	$\alpha$ angulation	0.982 (0.956,1.010)	0.202
	$\beta$ angulation	1.002 (0.975,1.029)	0.992
Reintervention (>30 days)	$\alpha$ angulation	0.990 (0.960,1.021)	0.510
	$\beta$ angulation	1.018 (0.987,1.050)	0.251
Mortality during follow up	$\alpha$ angulation	0.981 (0.960,1.003)	0.085
	$\beta$ angulation	0.992 (0.967,1.018)	0.562

For the outcomes; clinical failure, reintervention during follow up and mortality during follow up the variable  $\alpha$  angulation and  $\beta$  angulation have no statistical significance at the 2.5% level (the significance level has been adjusted by Bonferroni).

**Five- Year Survival Univariate Cox Proportional Hazards Model**

In the 5-year analysis there has been 32 events (deaths) out of 79 patients. The censoring time is 5-years survival and the cut-off point is 1826 days. Therefore, patients were either alive or dead at this point and were identified as such for the modelling. The following table depicts the results when fitting univariate Cox proportional hazards models to assess the relationship of different variables to 5-year survival. (see table 9.32)

**Table 9.32 5-Year Cox Proportional Hazards Model - Univariate**

Characteristics	Sub-group	5-Year Survival		
		Estimate (SE)	Hazard Ratio (95% confidence interval)	P-Value
Type of repair	(Baseline=EVAR)			
	fEVAR	-0.198 (0.494)	0.820 (0.312,2.159)	0.688
	Open	-0.260 (0.392)	0.771 (0.357,1.663)	0.507
Max aneurysm diameter		0.007 (0.014)	1.007 (0.979,1.036)	0.619
Neck length		0.015 (0.019)	1.015 (0.978,1.054)	0.419
$\alpha$ angulation		-0.007 (0.008)	0.993 (0.978,1.009)	0.404
$\beta$ angulation		-0.004 (0.009)	0.996 (0.979,1.014)	0.691
Max neck diameter		-0.017 (0.022)	0.983 (0.941,1.026)	0.432
% Oversizing		0.002 (0.033)	1.002 (0.939,1.070)	0.953
Number of IFU violations	(Baseline=1)			
	2	-1.094 (0.508)	0.335 (0.124,0.907)	0.031
	3	-0.544 (0.450)	0.580 (0.240,1.402)	0.227
	4	-0.693 (0.584)	0.500 (0.159,1.573)	0.236
	5	0.017 (0.771)	1.017 (0.225,4.609)	0.982
Gender	(Baseline=Female)			
	Male	0.470 (0.409)	1.604 (0.719,3.565)	0.250
Age		0.034 (0.024)	1.034 (0.987,1.084)	0.156

Table 9.32 – IFU – Instructions for use, SE – Standard Error.

At the 0.5% level (adjusted for Bonferroni correction) none of the variables are statistically significant.

**Five- Year Survival Multivariate Cox Proportional Hazards Model**

As there are only 32 events (deaths) and using the general rule of thumb for cox modelling stating that for each variable adding to a multivariate model 10 events are needed 3 variables were added for this data set. As none of the variables in the univariate model are significant those variables with the lowest 3 p-values were included in the multivariate model (see table 9.33).

**Table 9.33 - 5-Year Cox Proportional Hazards Model - Multivariate**

Characteristics	Sub-group	5-Year Survival		
		Estimate (SE)	Hazard Ratio (95% confidence interval)	P-Value
Number of IFU violations	(Baseline=1)			
	2	-1.106 (0.509)	0.331 (0.122,0.897)	0.030
	3	-0.513 (0.452)	0.598 (0.247,1.452)	0.256
	4	-0.574 (0.593)	0.564 (0.176,1.802)	0.334
	5	0.127 (0.776)	1.136 (0.248,5.194)	0.870
Gender	(Baseline=Female)			
	Male	0.046 (0.026)	1.047 (0.995,1.100)	0.075
Age		0.786 (0.428)	2.194 (0.948,5.076)	0.067

**Table 9.33 - IFU – Instructions for use, SE – Standard Error.**

At the 1.67% level (adjusted for Bonferroni correction) none of the variables are statistically significant.

These results suggest that of the variables identified in the cox proportional hazards model, none of them play a significant impact on whether the patient is alive at the 5-year time point for the studied population. Therefore, from this data set it is not possible to generate a risk prediction model for patients with non-standard aneurysms to determine the risk of death over follow up or at the 5-year time point.

#### 9.4.9. Comparison of Outcomes for Patients with a Standard Aneurysm

During the time period of the study (2006 – 2008) 232 patients were identified as having an aneurysm repair at the Royal Liverpool University Hospital. Of those patients 69 were non-standard and are included in the study above. In 2 patients there was disagreement between reviewers as to whether they were non-standard or standard and were therefore excluded. 65 patients had no preoperative scan available and therefore it is impossible to state whether they were standard or not. 11 patients identified suffered a ruptured aneurysm and therefore were excluded in line with the study methodology. 8 patients were treated for an aneurysm less than 55mm in diameter and again were excluded. For 31 other patients there were various reasons for exclusion – including previous aneurysm repair. This left 46 patients in whom there was an adequate preoperative CT scan that underwent repair of a standard aneurysm at the Royal Liverpool University Hospital. 39 patients underwent standard EVAR and 7 underwent open repair. Of the 39 patients who underwent standard EVAR 34 did so with a Zenith stent graft and in line with the above study these patients were included for further analysis along with the 7 open repair patients. The rest were excluded.

##### **Demographics of Standard Aneurysm Patients**

The majority of patients were male (87.8%) compared with 67.5% male patients in the non-standard group. The median age of the cohort was 73 (67 – 78), similar to the median age of 75 in the non-standard cohort. The following table details the demographics for all the patients grouped according to the type of operation performed and as a total for the whole group. (See table 9.34)

**Table 9.34 Patient Demographics for Standard Aneurysm**

Variable	EVAR (n=34)	Open Repair (n=7)	Total (n=41)	p-value
Age at operation (years), median (IQR)	75 (70,79)	65(62.5,68.5)	73(67,78)	0.005
Sex, n (%)				1.000
Male	30 (88.2)	6 (85.7)	36 (87.8)	
Female	4 (11.8)	1 (14.3)	5 (12.2)	
Previous Abdominal Surgery, n (%)				0.309
Yes	8 (23.5)	0	8 (19.5)	
No	25 (73.5)	7 (100)	31 (75.6)	
Unknown	1 (2.9)	0	1 (2.4)	
IHD, n (%)				0.031
No	7 (20.6)	4 (57.1)	11 (26.8)	
Yes	24 (70.6)	3 (42.9)	27 (65.9)	
COPD, n (%)				0.584
No	28 (82.4)	5 (71.4)	33 (80.5)	
Yes	5 (14.7)	2 (28.6)	7 (17.1)	
Unknown	1 (2.9)	0	1 (2.4)	
CVA, n (%)				0.552
No	30 (88.2)	6 (85.7)	36 (87.8)	
Yes	3 (8.8)	1 (14.3)	4 (9.8)	
Unknown	1 (2.9)	0	1 (2.4)	
DM, n (%)				0.656
No	24 (70.6)	6 (85.7)	30 (73.2)	

Yes	9 (26.5)	1 (14.3)	10 (24.4)	
Unknown	1 (2.9)	0	1 (2.4)	
<b>PVD, n (%)</b>				1.000
No	31 (91.2)	7 (100)	38 (92.7)	
Yes	2 (5.9)	0	2 (4.9)	
Unknown	1 (2.9)	0	1 (2.4)	
<b>Hypertension, n (%)</b>				1.000
No	8 (23.5)	1 (14.3)	9 (22)	
Yes	25 (73.5)	6 (85.7)	31 (75.6)	
Unknown	1 (2.9)	0	1 (2.4)	
<b>ASA Grade, n (%)</b>				1.000
1	0	0	0	
2	4 (11.8)	1 (14.3)	5 (12.2)	
3	29 (85.3)	6 (85.7)	35 (85.4)	
4	0	0	0	
Unknown	1 (2.9)	0	1 (2.4)	

Table 9.34 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry. IHD = Ischaemic Heart Disease. COPD = Chronic Obstructive Pulmonary Disease. CVA = Cerebrovascular Accident. DM = Diabetes Mellitus. PVD = Peripheral Vascular Disease. ASA= American Society of Anesthesiologists Grade.

The majority of patients were ASA grade 3 (85.4%). It is striking that there was a 10-year difference in the median ages between EVAR patients (75 years) and OR patients (65 years) with a statistically significant difference in this regard. Also 86% of standard patients were male compared to 67% of non-standard patients. Furthermore, significantly more patients who underwent EVAR had a history of ischaemic heart disease when compared with open

repair patients in the standard anatomy group. When comparing the difference between NSA and SA groups there was a statistically significant difference for the presence of IHD; 65.9% in SA patients, 45% in NSA patients ( $p= 0.0019$ ).

**Pre-operative investigations**

Parameters derived from pre-operative investigations were also collected for each patient. No patient was noted to be on renal dialysis pre-operatively and chronic kidney disease, as defined as having an eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$ , was present in 44% of all patients. (See table 9.35).

**Table 9.35 Pre-operative Investigations**

Variable	EVAR (n=34)	Open Repair (n=7)	Total (n=41)	p-value
Best FEV1, median (IQR)	2.4(1.9,2.8)	2.5 (2.4,3.8)	2.5 (2.1,2.8)	0.257
Creatinine (µmol/L), Median (IQR)	101 (85.3,112.3)	86 (70,108)	101 (82.5,111.5)	0.182
eGFR (ml/min/1.73m <sup>2</sup> ), median (IQR)	62 (51.8-72.8)	82 (59,97)	62 (54,80)	0.127
Chronic Kidney disease, eGFR <60				
None, eGFR ≥60 (%)	18 (52.9)	5 (71.4)	23 (56.1)	
Category 3a, eGFR 45 – 59 (%)	10 (29.4)	1 (14.3)	11 (26.8)	
Category 3b, eGFR 30 – 45 (%)	6 (25)	1 (14.3)	7 (17.1)	
Category 4, eGFR 15 – 29 (%)	0	0	0	

Table 9.35 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher’s exact test or  $\chi^2$  test, depending on the amount of data present in each entry. FEV1 = Forced expiratory volume in one second. FVC = Forced Vital Capacity. eGFR = Estimated Glomerular Filtration Rate.

When comparing the above values with those from the preoperative variables of non-standard patients – preoperative creatinine and eGFR levels were not statistically significantly different between the two anatomical groups. The mean best fev1 measured preoperatively was however significantly worse in NSA patients compared with SA patients (2.06 vs 2.43, p = 0.0156). Pre-operative CT scans were reviewed for all patients and various

anatomical data were collected for each patient. The following table summarises these data. (See table 9.36)

**Table 9.36 Aneurysm Morphology for Standard Patients**

Variable	EVAR (n=34)	Open Repair (n=7)	Total (n=41)	P – value
Max Aneurysm Diameter (mm), Median (IQR)	62.5 (59.3,70)	57 (56,81)	62 (57,72)	0.768
Neck Length (mm), Median (IQR)	29 (23,38.5)	25 (15,30)	28 (22.5,37.5)	0.152
Neck Diameter (mm), Median (IQR)	23 (21,27)	26 (24,27)	24(21.3,27)	0.199
$\alpha$ angle ( $^{\circ}$ ), Median (IQR)	17 (10.3,23.8)	16 (5,29)	17 (10,25)	0.831
$\beta$ angle ( $^{\circ}$ ), Median (IQR)	32 (17,47.5)	32 (20,40)	32 (17,46)	0.813
Expected clamp site, n (%)				NA
Infrarenal	34 (100)	7 (100)	41 (100)	
Suprarenal	0	0	0	
Supraceliac	0	0	0	

Table 9.36 - Comparison of continuous variables was carried out through a Kruskal-Wallis test (\*). Categorical variables were compared using Fisher's exact test or  $\chi^2$  test, depending on the amount of data present in each entry.

The smallest aneurysm in the series was 55mm in maximal diameter and the largest was 96mm. The median aneurysm diameter was 62mm, similar to that for the non-standard aneurysm cohort of 64mm. As would be expected the mean neck length, neck diameter , alpha angle and beta angle was different between the NSA and SA cohorts:

- Neck length – NSA 11.9 vs 29.2 SA ( $p = <0.001$ )
- Neck diameter – NSA 33 vs 23.4 SA ( $p = <0.001$ )
- Alpha angle – NSA 31.5 vs 18.3 SA ( $p = 0.005$ )
- Beta angle – NSA 43.1 vs 32.6 SA ( $p = 0.0104$ )

Maximum AAA diameter however was similar between the two anatomical cohorts with no statistically significant difference. Expected clamp site, as judged from the pre-operative CT scan, was infrarenal for all patients. Indeed all 7 open repair patients only had an infrarenal clamp placed as predicted.

All patients underwent their procedure in the operating theatre under general anaesthetic. No patient died intraoperative and there were no immediate conversions to open repair in the endovascular group. For those that received endovascular repair the device was placed under fluoroscopic guidance using a mobile C-arm in theatre. These variables were the same for non-standard and standard patients with the same equipment used.

#### **Comparison of Standard with Non-Standard Aneurysms**

For the principal outcome measures In hospital mortality, mid-term survival, aneurysm related mortality, technical success and clinical success statistical advice was sought to compare patients between types of repair (EVAR, Open repair) and type of aneurysm (non-standard and standard) to ascertain if there were any differences in these primary outcomes measures that could be attributed to either the intervention alone or the type of repair alone.

To do this the patients who had fEVAR from the non-standard aneurysm were removed from the dataset, so that this dataset can be compared with the standard dataset. The analysis therefore included 65 patients who had non-standard aneurysms (Open=37 and EVAR=28) and 41 patients who had standard aneurysms (Open=7 and EVAR=34). The two

datasets were merged into one. The outcomes of overall survival and clinical success cannot be calculated using a linear model as the outcome is not binary. The following table details the comparison for in hospital mortality (See table 9.37)

**Table 9.37 – Comparison of In hospital Morality**

Characteristic	Subgroup	In-hospital mortality	
		Alive at discharge (N=102)	Died in hospital (N=4)
Type of aneurysm, n (%)	Non-standard	61 (59.8%)	4 (100.0%)
	Standard	41 (40.2%)	0 (0.0%)
Type of repair, n (%)	Open	42 (41.2%)	2 (50.0%)
	EVAR	60 (58.8%)	2 (50.0%)

A generalised linear model was then fitted to the data, using the outcome of in-hospital mortality. Due to the number of events (deaths in hospital) being less than 10, the outcome is not robust, and a multivariate model is not appropriate. The type of aneurysm is used in the model, to see if there is a difference in in-hospital mortality over the 2 types.

**Table 9.38. - Univariate logistic regression model for the outcome in-hospital mortality**

Characteristic	Subgroup	Odd's Ratio (95% confidence interval)	P-value
Type of aneurysm	(Baseline=Non-Standard)		
	Standard	0.00 (0.00, ∞)	0.995

As can be seen from Table 9.38, the results are non-informative because there are no patients who died in hospital with standard aneurysms and overall there was less than 10 events. When comparing in hospital mortality the type of aneurysm does not play a

statistically significant role in whether a patient had a perioperative death or not within this cohort.

**Mid-term mortality outcome**

Mid-term mortality was calculated for patients who die between 5 and 10 years post-operatively. These patients who die are given the indicator = 1 and all other patients are given the indicator = 0. If patients are given indicator = 0, this does not mean they are alive, it just means they did not die in the timeframe stated. (See table 9.39)

**Table 9.39. - Comparison of Mid Term Mortality**

Characteristics	Subgroup	Mid-term mortality	
		Didn't die between 5-10 years post-op (N=67)	Died between 5-10 years post-op (N=39)
Type of aneurysm, n (%)	Non-standard	45 (67.2%)	20 (51.3%)
	Standard	22 (32.8%)	19 (48.7%)
Type of repair, n (%)	Open	31 (46.3%)	13 (33.3%)
	EVAR	36 (53.7%)	26 (66.7%)

A generalised linear model was then fitted to the data, using the outcome of mid-term mortality. The type of aneurysm is used in the model, to see if there is a difference in mid-term mortality over the 2 types. (See table9.40)

**Table 9.40 - Univariate logistic regression model for the outcome mid-term mortality**

Characteristic	Subgroup	Odd's Ratio (95% confidence interval)	P-value
Type of aneurysm	(Baseline=Non-Standard)		
	Standard	1.94 (0.87,4.36)	0.107

This analysis therefore reveals that the type of aneurysm is not statistically significant in predicting whether a patient died between 5 and 10 years. A multivariate model was produced to see the effects of type of repair. This included an interaction term. (See table 9.41)

**Table 9.41 - Multivariate logistic regression model for the outcome mid-term mortality**

Characteristic	Subgroup	Odd's Ratio (95% confidence interval)	P-value
Type of aneurysm	(Baseline=Non-Standard)		
	Standard	1.22 (0.44,3.37)	0.701
Type of repair	(Baseline=EVAR)		
	Open	0.50 (0.17,1.44)	0.199
Type of aneurysm *Type of repair		3.40 (0.48,24.12)	0.221

From Table 9.41, none of the variables are statistically significant to the outcome mid-term mortality, at the 5% level.

**Primary technical success outcome**

The following table investigates whether the type of repair or the type of aneurysm plays a significant role in technical success (See table 9.42)

*Table 9.42 – Comparison of Primary Technical Success*

Characteristics	Subgroup	Primary technical success	
		No (N=13)	Yes (N=93)
Type of aneurysm, n (%)	Non-standard	8 (61.5%)	57 (61.3%)
	Standard	5 (38.5%)	36 (38.7%)
Type of repair, n (%)	Open	2 (15.4%)	42 (45.2%)
	EVAR	11 (84.6%)	51 (54.8%)

Again, a generalised linear model (logistic) was fitted to the data, using the outcome of Primary technical success. Type of aneurysm is used in the model, to see if there is a difference in primary technical success over the 2 types. (See table 9.43)

*Table 9.43 - Univariate logistic regression model for the outcome primary technical success*

Characteristic	Subgroup	Odd's Ratio (95% confidence interval)	P-value
Type of aneurysm	(Baseline=Non-Standard)		
	Standard	1.01 (0.31,3.33)	0.986

The above table reveals that the type of aneurysm is not statistically significant at the 5% level for technical success. A multivariate model was produced to see the effects of type of repair. This included an interaction term. (See table 9.44)

*Table 9.44. - Multivariate logistic regression model for the outcome primary technical success*

Characteristic	Subgroup	Odds Ratio (95% confidence interval)	P-value
Type of aneurysm	(Baseline=Non-Standard)		
	Standard	2.50 (0.65,9.64)	0.183
Type of repair	(Baseline=EVAR)		
	Open	12.00 (1.38,104.40)	0.024
Type of aneurysm *Type of repair		0.07 (0.00,1.64)	0.097

The above table reveals that the type of repair is statistically significant for the outcome primary technical success, at the 5% level. This means from the odds ratio, patients who have an open repair are 12 times more likely to experience primary technical success. This is not dependent on what type of aneurysm they have, as can be seen from the interaction term being not statistically significant.

**Comparison of Renal Function**

Renal function changes over the longer term was also compared between standard and non-standard aneurysms to investigate this important secondary outcome measure in more detail. For standard aneurysm patients; the median eGFR change comparing preoperative eGFR with the last recorded eGFR was -18 (-24, -6) for open repair patients and was -13 (-21,3) for EVAR patients. This was not statistically significant with a p-value of 0.300. The following table documents the comparison of median change in eGFR between standard and non-standard aneurysms (See table 9.45)

*Table 9.45 - Comparison between the median change in eGFR (Last eGFR-Pre-op eGFR) for non-standard and standard aneurysms*

	Non-standard aneurysm	Standard aneurysm	P-Value
Change from baseline in eGFR, median (IQR)	-6 (-18,1)	-13 (-22,-1)	0.222

The table shows that although the median eGFR reduction is greater for standard aneurysm patients this difference is not statistically significant

Change in eGFR was compared for EVAR and open repair patients separately for non-standard patients and standard patients. (See table 9.46)

*Table 9.46 - Comparison between the median change in eGFR (Last eGFR-Pre-op eGFR) for non-standard and standard aneurysms*

	Non-standard	Standard	P-value
<b>Open Repair</b>			
Change from baseline in eGFR, median (IQR)	-3 (-17,2)	-18 (-24,-6)	0.091
<b>EVAR</b>			
Change from baseline in eGFR, median (IQR)	-10 (-22,-2)	-13 (-21,3)	0.810

As can be seen from the above table there is no statistically significant difference between either open repair or EVAR when comparing standard with non-standard aneurysms.

## 9.5. Summary of Results

The following tables summarise the principal outcomes for non-standard and standard patients from the above study and from the literature reported earlier. (See tables 9.34 and 9.47)

**Table 9.47 – Reported Outcomes for NSA AAA from multicentre retrospective cohort study and Literature**

Treatment	Primary Technical Success (n)	Perioperative mortality (n)	5-year survival (n)	Aneurysm Related Mortality (n)	Renal Dysfunction (n)
<b>Multicentre Retrospective Cohort Study</b>					
fEVAR	100%* (15)	0%	57% (8)	0%	13.3% (2)
EVAR	82%* (23)	7.1% (2)	54% (15)	10.7% (3)	50% (14)
Open Repair	97.3% (36)	5.4% (2)	68% (25)	8.1% (3)	24.3% (9)
<b>Total</b>	<b>92.5% (74)</b>	<b>5% (4)</b>	<b>61% (48)</b>	<b>7.5% (6)</b>	<b>31.3% (25)</b>
<b>Literature</b>					
fEVAR <sup>a</sup>	95.6%*	2.7%	59.4 – 92%	0.8%	21 – 27%
EVAR	90.7%	3.1%	70 – 85.4%	0 – 6.8%	-
Open Repair	NR	3.2%	64 – 88.6%	1.3%	11.3%

*Table 9.47 – fEVAR – fenestrated endovascular aneurysm repair EVAR – Endovascular Aneurysm Repair. Renal dysfunction is the rate reported over long term follow up. A – The results for fEVAR are collated from the systematic review of 8 studies published since 2015. \* - Adjusted Primary Technical success as reported by Roy et.al.*

The table collates principle outcome measures for the three treatment options from the study and the literature. The adjusted primary technical success rate as described by Roy

et.al. accounting for those patients with a graft related endoleak on completion angiogram that spontaneously seals without clinical sequelae is reported in the above table. In all cases a value is given for aneurysm related mortality but, as stated above, there were a number of patients in the retrospective study in which limited information meant that the true value of aneurysm related mortality was not known. However, the above reported values are the minimum possible true value for aneurysm related mortality (i.e. the 6 deaths for the cohort are definitely aneurysm related). The results for aneurysm related mortality from the literature were inconsistently reported and similarly a limited conclusion can be drawn from these numbers. The definition of renal dysfunction varied between studies and the primary definition of a drop in CKD grade as described above was used to calculate the values in the above table. With all that being said the results for fEVAR between this study and the literature are fairly similar on all counts. For EVAR the values reported within the study appear to be worse on all counts compared with the literature, suggesting significant heterogeneity between the population being studied and the wider literature. IT is not clear exactly where this may be from. With regards to open repair the results appear worse for aneurysm related mortality and renal dysfunction in the study compared with the literature but similar in terms of perioperative and long-term mortality. The following table documents similar findings for standard aneurysms from both the study and the literature (See table 9.48)

*Table 9.48 - Reported Outcomes for SA AAA from multicentre retrospective cohort study and Literature*

Treatment	Primary Technical Success (n)	Perioperative mortality (n)	4-year survival (n)	Aneurysm Related Mortality (n)	Renal Dysfunction (n)
<b>Single Centre Retrospective Cohort Study</b>					
EVAR	88% (30)	0%	71% (24)	0%	53% (18)
Open Repair	86% (6)	0%	100% (7)	0%	43% (3)
<b>Total</b>	88% (36)	0%	76% (31)	0%	51% (21)
<b>Literature</b>					
EVAR	NR	1.4%	84.2%	2.9%	-
Open Repair	NR	4.2%	83%	4.3%	-

*Table 9.48. EVAR – Endovascular Aneurysm Repair*

Little can be said about the comparisons between open repair and EVAR for the single centre retrospective study and in comparison, to the literature, primarily because the numbers of patients undergoing open repair especially were so small. However, of note the 4-year survival (4 year chosen because this is what was represented in the literature) for EVAR for standard aneurysm patients was lower than that reported in the literature and was actually in line with the 5-year survival for NSA patients undergoing EVAR. The small sample size may play a role in this finding but 88% of the population of EVAR patients with SA were ASA grade 3. For all studies in the systematic review investigating outcomes after standard EVAR the proportion of patients with ASA grade 3 or 4 ranged between 50 – 100% with their SA counterparts at least the same if not “fitter” than this. Therefore, the increase in long term mortality may be related to this cohort of patients with a seemingly higher ASA grade at the outset.

## **10. CHAPTER 10 – Discussion of Retrospective Multicentre and Single Centre Cohort Studies**

The aim of this study was to compare outcomes of conventional surgery, EVAR outside IFU and fEVAR for non-standard aneurysms within a defined geographical region, in terms of risk-adjusted perioperative mortality, major perioperative complications, clinical success and mid-term survival. This was to test the hypothesis, which was: Fenestrated Endovascular Aneurysm Repair (fEVAR) has the best clinical outcome as a treatment strategy for non-standard AAAs that are unruptured in whom aneurysm repair is deemed to be more beneficial than conservative management.

### **10.1. Primary and Secondary Outcome Measures**

The primary outcome measures were: in-hospital mortality, longer term overall survival, longer term aneurysm related mortality, technical success and clinical success. The secondary outcome measures were: Visceral vessel patency, renal insufficiency and need for dialysis, re-intervention rates (including conversion to open repair) and major complications. The following table demonstrates the results for these outcome measures alone comparing the three treatment options: (See Table 10.1)

*Table 10.1 Primary and Secondary Outcome Measures*

Outcome measure	EVAR (n=28)	fEVAR (n=15)	Open Repair (n=37)	Statistically significant difference
In hospital mortality	7.1%	0%	5.4%	
Overall Survival (at 5 years)	54%	57%	68%	
Aneurysm Related mortality	10% +	0%	8% +	
Technical success	75%	87%	97%	P <0.001
Clinical Failure	46%	7%	8%	P <0.001
Visceral vessel occlusion	4%	0%	0%	
Renal insufficiency, AKI In-Hospital	25%	20%	43%	
Renal Insufficiency, Change of CKD grade	50%	13.3%	24.3%	
Dialysis	0%	0%	0%	
Reintervention rates (in-hospital)	14%	0%	8%	
Reintervention rates (long term)	25%	13.3%	8%	
Conversion to open repair	11%	0%		
Major complications (in hospital)	14%	7%	54%	

As can be seen from the table patients who underwent fEVAR, within this cohort, had the best clinical outcomes, as defined by the primary and secondary outcome measures, when

compared with the other two treatment methods. However, it must be noted that this apparent 'advantage' of fEVAR did not reach statistical significance when comparing it against the other two treatment methods in any outcome measure. The apparent 'disadvantage' of the other treatment methods was only recorded as statistically significant for two outcomes: technical success and clinical failure – with EVAR performing the worst of the three, especially in clinical failure

Despite the limited numbers in this study, especially of fEVAR patients, it is still the method of repair with the most favourable clinical outcomes in this cohort. Also, the lack of numbers acts to minimise potential statistically significant differences between the groups: in hospital mortality, aneurysm related mortality, reintervention rates and conversion to open repair. It seems plausible if a larger cohort of fEVAR patients were to exhibit similar outcomes then statistical significance would be reached. Chapter 8 detailed the clinical outcomes for patients who underwent fEVAR at the Royal Liverpool University Hospital over a longer period than the current study. The following table compares the primary and secondary outcome measures between the larger cohort detailed in chapter 8 with the patients that underwent fEVAR in the current study. It should be noted that all 15 patients in the current study were also included in the larger study also. (See table 10.2)

*Table 10.2 Primary and Secondary Outcome Measures for fEVAR patients from the Current Study and Larger fEVAR study at the Same Institution*

<b>Outcome measure</b>	<b>fEVAR (current study, n = 15)</b>	<b>fEVAR (larger study, n = 107)</b>
<b>In hospital mortality</b>	0%	3.7%
<b>Overall Survival (at 5 years)</b>	57%	53%
<b>Aneurysm Related mortality</b>	0%	0%
<b>Technical success</b>	87%	86%
<b>Clinical Failure</b>	7%	-
<b>Visceral vessel occlusion</b>	0%	6%
<b>Renal insufficiency, Change of CKD grade over FU</b>	13%	-
<b>Dialysis</b>	0%	0%
<b>Reintervention rates (in-hospital)</b>	0%	7%
<b>Reintervention rates (long term)</b>	7%	24%
<b>Conversion to open repair</b>	0%	0%
<b>Major complications (in hospital)</b>	7%	-
<b>Major complications (Long term)</b>	0%	-

The results, as detailed in chapter 8, show that: in-hospital mortality after fEVAR was 3.7%, still less than both standard EVAR and OR in the current study. Aneurysm related mortality was still 0% with a median follow up of 51 months (Range: 1 - 124). Conversion to open repair amongst 107 fEVAR patients was 0% and 7% of patients underwent in-hospital reintervention, in line with the results from the current study. This therefore suggests that the difference seen in absolute values would be unlikely to differ much for these parameters if more fEVAR patients were included in the current study.

Regarding the hypothesis of this study - there are many facets of what would constitute the 'best clinical outcome' and therefore it is important to interrogate these areas in more

detail individually to build up a picture of and be able to synthesise an answer to the question posed.

### **10.1.1. In Hospital Mortality**

Patients who underwent fEVAR had a 0% in hospital mortality rate within this study. Although this apparent advantage of fEVAR compared with OR and EVAR did not reach statistical significance this is still a striking result. There are limited numbers within this study, especially of fEVAR patients, so this finding may be due to chance. The reduction in perioperative mortality is one of the central advantages of endovascular repair compared with OR. This has been shown in numerous randomised controlled trials and studies comparing standard EVAR (within IFU) with OR [71, 72, 77, 183-185] and one study that compares fEVAR with OR [170]. Another study by Chisci et. al. showed no significant difference in perioperative mortality in patients undergoing fEVAR compared with OR.[121] There is therefore a paucity of data comparing EVAR, fEVAR and OR for non-standard aneurysms, and in the one study in the literature (above) and the current study, no significant differences in perioperative mortality have been found and the results for those two cohorts of patients were at odds with each other, suggesting that neither study has adequately determined the true risk of perioperative mortality in these patient groups.

The systematic review of the recent literature detailing outcomes from fEVAR reported above in Chapter 7 reported perioperative mortality ranges from 0.7 – 5.2% in the included studies. The pooled mortality rate for all the included studies was: 2.7%. One study by Verhoeven et.al. [157] included fEVAR as a “first-line” treatment and admits to treating a large number of “low risk” patients with fEVAR. The perioperative mortality rate in that study is 0.7%. The authors comment that fEVAR is used as a first line treatment options rather than specifically being selective of low risk patients, though this is essentially what it amounts to in the final analysis. That study shows that, albeit in expert hands, fEVAR can be

performed with an exceedingly low risk of perioperative mortality. AN important finding when comparing patients with those undergoing open repair which, when outcomes are reported for all patients from any given centre, tend to be those patients who are deemed to be “fitter” preoperatively.

Although the results presented show open repair had a higher perioperative mortality rate compared with fEVAR the published literature does detail that OR can be performed safely with a lower rate of perioperative death than seen in the current study. The perioperative mortality rate reported in the systematic review above (Chapter 6) investigating the outcomes of NSA patients undergoing open repair details rates between 0.8 and 6%. The total combined perioperative mortality for all studies was 37 patients out of 1150 (3.2%).

The results also showed a higher perioperative mortality rate for patients undergoing EVAR however the literature shows that patients who undergo standard EVAR in compromised anatomy perioperative mortality does not tend to be sacrificed but other clinical outcomes are. The literature documents the danger of placing standard EVAR within a less than ideal infrarenal neck; increased angulation and decreased neck length being associated with increased incidence of proximal type 1 endoleaks, increased need for intraoperative adjunctive manoeuvres, and a reduction in initial technical and midterm clinical success [67, 68, 122, 186], one of these studies by Leurs et.al. [68] does show a significantly increased perioperative mortality rate in those with a neck length <15mm compared with those >15mm, however there are limitations to this study in determining the outcome of those patients who are outside of IFU as neck length was the only determinant of selection for one group or another patients may have other factors that place them outside IFU in the >15mm neck length group, thereby limiting the conclusions that can be drawn from the analysis. However, it would be reasonable to suggest that if all patients who were out of IFU were excluded from the >15mm neck length group then the mortality of that group

would, at least, be no worse. This remains the stand-alone study that shows a difference in perioperative mortality however.

The literature and the current study therefore fail to show convincing evidence to suggest the improvement in perioperative mortality associated with endovascular repair seen with standard aneurysms is applicable for non-standard aneurysms. There is also little evidence to suggest that perioperative mortality is significantly higher in those undergoing OR for these complex non-standard aneurysms. However, as stated, there is a lack of direct comparative studies of sufficient calibre and with sufficient numbers of patients to conclude that there is no benefit whatsoever.

What was not clear during this retrospective study were the reasons why the physicians elected to place a standard EVAR device as opposed to fEVAR as each patient, by definition, was a less than ideal candidate for standard EVAR. One reason may be that these were grossly enlarged or symptomatic aneurysms that would be better served by a timely repair rather than incurring a delay of up to three months to wait for manufacture and delivery of the bespoke fenestrated device. However, all aneurysms in this study were asymptomatic and any patients in whom there was a suggestion from the clinical case notes that aneurysm related symptoms were present were excluded from the study, so this seems unlikely. Furthermore, although it was true that aneurysms within the EVAR cohort were larger overall compared with fEVAR patients, the difference was not so great to account for the preference of EVAR in most cases; the median aneurysm diameters were 66mm for EVAR and 60mm for fEVAR patients. There were only seven patients (24%) in the EVAR group who had an aneurysm diameter of >70mm and only two >80mm. What is apparent from the results is that the aneurysms within the EVAR group had simpler anatomy than that of the fEVAR group (Longer, narrower necks, less number of IFU violations for each case) and it is likely that the physicians assessing these cases simply did not ascribe these

characteristics that are outside of IFU but 'not too bad' a significant level of importance to warrant placing a more complex fenestrated device, especially with the additional costs and constraints placing such a device has. To clarify, during the time period studied these devices were funded only on an individual case by case basis and as such more delays and difficulties were present from an organisational level in using them. Therefore, it is not obvious that the increased mortality rate with EVAR seen in this study compared with fEVAR was simply due to more 'acute' aneurysms being treated quickly to prevent rupture.

It is also unknown whether there were any patients that died as a result of the inherent delay incurred in the decision to treat with fEVAR secondary to rupture of their aneurysm. Although this effect is likely to be small if present at all it would be important to quantify and analyse this in any future research. The aim of this study is based on trying to answer the question of which type of repair should be offered to a patient who presents with an unruptured aneurysm. There would be no point in recommending fEVAR over everything else if once the decision is made in the outpatient department to treat by fEVAR a significant proportion of patients die while waiting 3 months for their repair. Future research would ideally be a prospective study following up all patients who present with such aneurysms from the pre-operative time-point. This would therefore help clarify whether rupture in the intervening period between initial assessment and operation is a disadvantage with selecting this method of repair.

In terms of perioperative mortality there was no advantage in performing fEVAR over either other method of repair. This also seems confirmed by the published literature failing to consistently show a significant advantage in performing fEVAR or disadvantage in performing EVAR or OR for non-standard aneurysms, with regards to perioperative mortality. There remains a lack of direct comparative evidence however to state this definitively.

### 10.1.2. Overall Survival

Of 80 patients, there was only one in whom it was not possible to identify if they were still alive or not. That patient underwent a successful fEVAR operation with no significant complications during their inpatient stay or up to one-year post operatively. The patient attended for their one-year post-operative surveillance which did not identify any problems but subsequently emigrated after that. It was not possible to contact the patient as no forward address or telephone number was available. That patient was considered alive at their last follow up time point and censored after that. In every other case it was possible to identify from a variety of sources whether the patient was still alive and if not the date of death was obtained. There were a handful of cases that were not local to the region in which they were treated, and, in each case, their general practitioner was contacted to confirm if they were still alive or not. With a median follow up of 10 years there was no statistically significant difference in the survival experience of the patients over the follow up period. The overall survival at 5 years was between 54 and 68% depending on the type of repair received. Although this value seems low it is in line with other published results of aneurysm repair patients with a similarly long follow up time. [77, 84, 175, 187] The fact is that patients with advanced aneurysmal disease represent a patient cohort at the severe end of the spectrum of cardiovascular disease. These patients often have coexisting medical conditions, such as ischaemic heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, hypertension, and exhibit advanced age at presentation. According to the office for national statistics the current life expectancy in the UK for males aged 65 years is 18.3 years and for females aged 65 it is 20.8 years. [188] Considering that these statistics from the ONS include all people within the population at 65 years and the cohort of patients within this study are 75 years old on average and represent a specific cohort of unhealthy individuals it should be unsurprising that after 5 years roughly half of these patients are dead.

Although a significant difference was not seen in this study there was a trend towards worse overall survival in the EVAR cohort of patients. The patients undergoing endovascular repair in this study were less fit than their counterparts undergoing OR, with a higher ASA grade and this may in part explain the trend to worse overall survival in these patients. Interestingly however fEVAR patients had a significantly greater incidence of ischaemic heart disease but despite this they did not show a significantly increased chance of suffering post-operative complications of any type and specifically of a cardiac nature as one may have expected, especially when compared with their endovascular counterparts undergoing standard EVAR. Although no firm conclusions can be drawn from this data due to the limitations of this study these results do suggest that with reference to long term survival there does not appear to be an advantage of any one type of repair over another. Therefore, the traditional viewpoint that younger, fitter patients should undergo open repair as the upfront risk of increased perioperative mortality is offset by the longevity of the repair is not borne out by this data.

The survival experiences of patients did not significantly differ within this study and therefore the decision of which type of operation a patient with a non-standard aneurysm should have should not be based upon an expectation of advantage in long term survival with one method of repair compared with another.

### **10.1.3. Aneurysm Related Mortality**

Unfortunately, it was not possible to garner the cause of death for every patient within this cohort. There were 57 deaths during the study period, four were in hospital mortalities and a further two were aneurysm related deaths as detailed in the results section. Where a death certificate had been issued and was available the cause of death cited on the certificate was taken as the patient's cause of death (19 patients). If there was evidence that a post mortem examination was carried out then the results of this, where available,

were taken into consideration when deciding the cause of death (2 patient). If either of these sources were not available, the clinical case notes were scrutinised and if the patient's death was within hospital then an assumption of whether the cause of death was aneurysm related or not was made based upon the clinical details for that period of care leading up to the patient's death (12 patients). If the death was not in hospital and the clinical case notes did not reveal the cause of death the GP was contacted to try and ascertain the cause. However, this did not give any more information pertaining to the cause of death in any case. There were therefore 18 cases where the cause of death was unknown. In all cases of fEVAR the cause of death was known.

Since not all patients had a known cause of death it was not appropriate to analyse aneurysm related mortality further. However, it can be seen that there was no aneurysm related mortality in the fEVAR group and at least 10% of patients in the EVAR group and at least 8% in the OR group suffered an aneurysm related mortality. It is true that the majority of aneurysm related deaths were in hospital deaths after the primary procedure but in one case in the EVAR group a patient suffered a ruptured aneurysm after failure of the device occurred in the form of migration and type 1 endoleak. In the case of OR there was one patient that died nearly 6 years after his operation following massive gastrointestinal haemorrhage from an aortoenteric fistula secondary to an infected prosthetic aortic graft. It should be noted that this complication is not necessarily specific to OR and in fact has been seen with endovascular prostheses too. [189]

The apparent advantage of fEVAR in relation to aneurysm related mortality seen in this study therefore appears to derive again from its lower perioperative mortality rate more than anything else. The case of the EVAR patient who exhibited migration further reinforces the idea that an endovascular device placed outside IFU may be prone to device

failure and this case is a potent reminder of the catastrophic consequences that can result from such a failure.

The fact that no migration was seen within the fEVAR cohort compared with nine patients in the EVAR cohort ( $p= 0.017$ ) reiterates the potential for device failure when EVAR is placed outside of the IFU.

Aneurysm related mortality was poorly and inconsistently reported in the literature with some studies simply reporting deaths during follow up that were aneurysm related. Other studies reported deaths that were aneurysm related as a proportion of the whole patient cohort, the patient cohort surviving their index admission and a variety of other methods. It was this authors inclination to adopt the reporting standards definition of aneurysm related mortality and include any death within the index hospital admission or after any reintervention for aneurysm related issues as aneurysm related mortality, including those patients who were clarified as having ruptured. One way to report aneurysm related mortality would be Kaplan-Meier analysis of freedom from aneurysm related mortality with the above definitions and although not done in this study is recommended by this report as a more robust and consistent way of documenting the rates of aneurysm related mortality.

#### **10.1.4. Technical Success**

Although the rate of technical success, as defined by the reporting standards [93], was less in the group who received EVAR and the difference across the three groups was found to be significantly different, the rate was similar to that of technical success in the fEVAR group. The patients who underwent OR enjoyed a very high technical success rate of 97%. However, when scrutinising the reporting standards, it is apparent that the definition of technical success used is different for endovascular repair compared with open repair. This is because the method of repair and therefore potential failure mechanisms during the immediate phase after aneurysm exclusion are inherently different. Also, the reporting

standards are specifically designed for endovascular aneurysm repair and define the qualifying details for technical failure for OR more out of completeness rather than a desire to accurately compare the two treatment methods. Technical success for endovascular repair requires “successful introduction and deployment of the device in the absence of surgical conversion or mortality, type I or III endoleaks, or graft limb obstruction” furthermore if unplanned endovascular procedures are undertaken then this disqualifies the use of the term primary technical success. [93] Technical success for open repair requires “replacement or bypass of the aneurysmal segment with a prosthetic graft in the absence of mortality or graft thrombosis either during surgery or during the initial 24-hour postoperative period” and if an unplanned surgical procedure is performed then this disqualifies the use of the term primary technical success[93]. The main difference between the two definitions of technical success therefore is the requirement of endovascular repair to be performed without a type I or III (graft-related) endoleak at the end of the operation. A graft-related endoleak is one where there is continued perfusion of the aneurysm either by: a persistent “perigraft channel of blood flow due to inadequate or ineffective seal at the (proximal or distal) graft end” (type I endoleak) or, “at the midgraft region due to leakage through a defect in the graft fabric or between segments of a modular...graft” (type III endoleak)[190]. It is known that Type I endoleaks in general are associated with increased sac pressure and aneurysm expansion, and have been shown to be a significant risk factor for late aneurysm rupture and open conversion[66, 191]. This data relates to type I endoleaks in general, i.e. those that develop after aneurysm repair, and it is because of this data and a consensus that type I endoleaks will not seal spontaneously [192] that they have been considered a potentially fatal complication of endovascular repair if noted during the operation, hence the importance placed upon them in determining if a case is technically successful or not. The significance of type I endoleaks at the end of an endovascular procedure however has been questioned with literature

suggesting that the majority of patients with a type I endoleak at the end of an EVAR operation will spontaneously seal their endoleak. [193] Indeed in this cohort of patients; the two patients who exhibited technical failure in the fEVAR group were because of a type I/III endoleak at the end of the operation. In both cases the endoleak spontaneously sealed without adverse event or secondary intervention. In the EVAR group, four patients had a type I endoleak at the end of their operation and two of these patients spontaneously sealed their endoleak without reintervention or adverse event. Roy et.al. [160] and the registry data report from the GLOBALSTAR collaborators [82] utilise the term adjusted primary technical success rate to allow for those patients with an endoleak that spontaneously seal without consequence and when utilising this definition for the above study technical success rates of 92.9% and 100% for EVAR and fEVAR respectively were reached. The use of primary technical success with the qualifier of adjusted technical success is a sensible and useful one primarily because it appears that those patients who have a small endoleak on the day of surgery that then seals within days or weeks progress (in terms of aneurysm relate outcome events) the same as patients who never had an identifiable endoleak. Furthermore, as imaging equipment and resolution of viewing screens improves the ability for clinicians to identify small, low flow endoleaks today is much improved compared to when fEVAR became widespread in its use (2001 – 2008). It is also probable that within the literature there are reports that chose to define primary technical success in the same way the above study has defined adjusted primary technical success but without explicitly mentioning it. The only way that we can be certain that these low flow, self-resolving endoleaks truly are as benign as they seem is for the entire community to report their presence.

In addition, although technical success is important to record and report for any operation it may not be wise to use it to compare treatment methods with differing definitions of technical success. It can be seen that in patients with non-standard aneurysms each of the

three treatment options can be performed with high rates of successful completion of the operation without significant immediate sequelae.

#### **10.1.5. Clinical Success**

There was a statistically significant difference in terms of clinical failure across the three groups with standard EVAR showing significantly worse outcomes in terms of clinical success/failure. The measurement of clinical success, as defined within the reporting standards [93] gives an overall picture of the longitudinal experiences of each patient cohort with regards to clinically relevant events. The striking feature seen in this analysis is the sharp downward trend that continues throughout the follow up for patients within the EVAR group, but it should be noted that clinically relevant events such as migration of the stent graft >5mm is included in the definition of clinical failure. Although this is relevant and important as it can herald the onset of a significant graft-related endoleak which could ultimately lead to aneurysm rupture and therefore catastrophic failure of the stent-graft it is by no means certain that this will happen. Indeed, within the EVAR cohort of patients there were three patients classified as clinical failures because of migration; one was alive at the last follow up time point with a shrinking aneurysm, one more died of non-aneurysm related causes and had a shrinking aneurysm at last follow up surveillance scan, both didn't demonstrate an endoleak throughout their follow up (9 and 5 years after migration first noted). The other patient had migration first noted 2 years after the index procedure and then over the next 2 years demonstrated progressive loss of seal with neck dilatation but no proximal endoleak. The patient died secondary to malignant disease at that point.

These cases demonstrate that it is quite difficult to define exactly what constitutes a clinical failure or continued clinical success. One method to counter this issue would be to analyse clinical failure in a hierarchical fashion by assigning certain methods of failure such as aneurysm related mortality an increased level of importance compared to migration alone. That would allow a certain amount of adjustment for those that represent

undeniable clinical failure (aneurysm related death, open conversion) with those that only represent a risk of undeniable clinical failure (graft related endoleak, migration). This however would need further research and statistical input to determine whether this was a valid and useful way of monitoring clinical success, which is beyond the scope of the current work.

There are two facets to the measurement of clinical failure of aneurysm repair in the sense that it can be treatment centred or patient centred. Treatment centred would describe clinical failure in any patient who is considered to have failure of the treatment by predefined failure mechanisms as described in the published reporting standards. Patient centred clinical failure would take account of the initial aim of the treatment (to reduce the risk of the aneurysm rupturing) and secondary aims (to do so without causing death or disability) so that only events which have an impact on the patient are considered. The advantage of treatment centred measurement of clinical failure is that it can give a more accurate picture of the performance of a given treatment to allow the generalizability of how that specific treatment is expected to perform in any given population. The disadvantage is that it may class certain cases as clinical failure in which there potentially will be no consequences of the said 'failure' what so ever. Therefore, the main difference is that treatment centred will tend to over-report clinical failure whereas patient centred will tend to under report it. When the clinical failure in question is death or 'risk of death' it may be wiser to choose the method which over-reports its occurrence. Although the methods for measuring clinical failure are not perfect, they provide a reasonable assessment of how each method of repair performs within a patient cohort longitudinally and these results have shown clear inferiority with standard EVAR in this regard.

#### 10.1.6. Visceral vessel occlusion

Fenestrated stent-graft technology is unique from the other methods of repair in one respect – the incorporation of visceral vessels (Renal, superior mesenteric and coeliac arteries) into the repair. Both OR and standard EVAR have only indirect effects on the visceral vasculature whereas fEVAR, by its nature, demands endovascular access and stenting of visceral (target) vessels. Furthermore, the stents are an inherent part of the repair and as such remain in place for the life of the repair. It is true that in some circumstances the visceral vasculature would be incorporated into open repair by either bypass or reimplantation of the vessels during the initial repair, this however is usually only necessary when the aneurysm extends around and above the renal arteries in what would therefore constitute a type 4 thoracoabdominal aneurysm. This type of aneurysm was excluded from this study because it represents a distinct aneurysmal entity that, if repaired by endovascular means, would require entirely different technology, namely branched endograft technology. On occasion a pararenal or juxtarenal open aneurysm repair may require that a renal artery is reimplanted during the procedure because of complication or specific anatomical anomalies, however this was not true for any patient in this cohort.

Since the introduction of fEVAR the increased exposure to a potential risk of target vessel loss has been an area of concern and perceived disadvantage of this method of repair. However, this potentially catastrophic complication has not been reported commonly in patients undergoing fEVAR with target vessel patency rates of 95% at 3 years in one large series. [82] In fact in the current study there were no target vessel losses noted at any point in the fEVAR group. There were also none recorded in the open repair group either, but it should be noted that this group of patients do not routinely undergo follow up scanning which could determine whether any visceral vessels had occluded during follow up. Target vessel loss with fEVAR is therefore relatively rare and even when it does occur it does not seem to have catastrophic consequences. In this study, there was also one patient who

suffered occlusion of a renal artery after standard EVAR highlighting that the risk of this particular complication is not solely experienced by those who undergo fEVAR.

With regards to visceral vessel patency there is therefore no advantage, but importantly also, no disadvantage with fEVAR compared with the other repair options, as seen from the results in this study and from the wider published literature.

#### **10.1.7. Renal Insufficiency (Long term)**

Although no patients suffered renal dysfunction to a degree where long term dialysis was required patients who underwent EVAR did demonstrate worse renal function over the long term. There was also no significant difference in terms of the occurrence of acute kidney injury between the three repair types during the in hospital stay though open repair patients suffered it more often (43% vs 20 and 25%). Despite this it was the EVAR cohort of patients that demonstrated the largest occurrence of deterioration in renal function as measured by CKD stage deterioration and change in eGFR; 50% of EVAR patients had a deterioration in their CKD stage at some point during follow up (compared with 13% of fEVAR and 24% of OR patients). This didn't reach statistical significance however. The minimum eGFR postoperatively was reached at a median of four years from the operation (Range; 3 months – 6 years). The definition used in this study of deterioration of CKD stage seems sensible but may not be the most clinically relevant. As discussed above a patient would be classed as renal insufficiency over the long term by this definition if their eGFR dropped from 61 to 59, which may not be clinically relevant. It may be argued that this excess of renal insufficiency in EVAR patients was simply due to this 'low-level' renal deterioration. However when analysing if a patient dropped two stages (representing a drop from 61 to 44) EVAR patients still more commonly suffered this (18% of patients vs 7% for fEVAR and 11% for OR). Again this didn't reach statistical significance it should be noted. The fact that EVAR patients demonstrate worse renal function over the longer term is

interesting and somewhat surprising as this is the group that, theoretically, has the least invasive intervention in terms of potential or actual disruption to the renal vasculature. fEVAR involves direct cannulation and stenting of the renal arteries and a significant proportion of patients undergoing OR (30%) had a clamp placed above at least one of the renal arteries. There was no significant difference between the three groups in terms of; pre-operative renal function, presence of hypertension or diabetic disease, which could have accounted for deterioration in renal function. There was also no significant difference in terms of in-hospital renal function, and in fact OR performed worse in this regard, suggesting that the deterioration in renal function seen in the EVAR group is attributable to events after the primary operation and hospital admission. One explanation for the deterioration in renal function may be that patients who underwent EVAR had more reinterventions over the longer term. The increased burden of secondary procedures and their potential detrimental effect on renal function is a plausible reason for the decrease seen in renal function especially since three patients underwent conversion to open repair and one further patient underwent an anterior resection and left nephrectomy, which was unrelated to the EVAR procedure and had been planned before the aneurysm repair. Furthermore, patients who underwent EVAR had a higher burden of thrombus within the infrarenal neck compared with the other two groups. This however did not reach a statistical difference. It is possible that microembolisation of thrombus within the infrarenal neck to the kidneys could have occurred causing renal dysfunction. However, if this was the case one would expect to see a significant rise in the creatinine for this complication within the first few days to week (i.e. the in hospital stay) after the operation. As already stated, this was not the case in any of the groups. Another explanation could be that stenting of the renal arteries in the fEVAR group provides some protection to renal blood flow over the long term and therefore some protection and preservation of renal

function. There is little evidence to support this theory however especially considering that OR patients exhibited maintenance of their renal function without renal stenting.

It is unfortunate that there was no data available relating to the amount of iodinated contrast used either during the primary or secondary procedures as it would be important to assess whether there was any relationship between the use of contrast and deterioration in renal function. It is however unlikely that this in itself would be an explanation for the worse renal function seen in the EVAR group, for two reasons: Firstly, fEVAR utilises contrast media also but the procedures tend to be more prolonged and with the additional complexities of target vessel cannulation and stenting there is often larger volumes of contrast medium used in these cases. Secondly, as stated, the deterioration in renal function occurred long after the initial procedure making a causal link unlikely. In addition, the increased contrast burden of surveillance scans is experienced mainly by fEVAR patients as they routinely underwent annual CTA as part of their surveillance and the EVAR patients only underwent selective CTA.

These findings do not suggest superiority of fEVAR but rather inferiority of standard EVAR for the treatment of non-standard aneurysms. It is true that no patient went on to require dialysis as a result of their renal dysfunction but the detrimental effects of chronic kidney disease should not be underestimated either as patients with chronic kidney disease have an elevated risk of death, cardiovascular events and hospitalisation compared with those with normal renal function [194, 195].

#### **10.1.8. Reintervention Rates**

There was no statistically significant difference across the three groups in terms of the number of patients requiring in-hospital reinterventions or any reintervention post discharge.

When comparing methods of aneurysm repair secondary intervention is an important outcome to assess, particularly as an oft quoted disadvantage of endovascular repair is the increased need for reintervention. In this study there was no significant difference in the proportion of patients needing a reintervention at any time with 25% of EVAR patients, 13% of fEVAR patients and 8% of OR patients requiring at least one reintervention over the longer term. As can be seen the reintervention rate after EVAR is higher than fEVAR or OR, but in line with other reported studies, especially for NSA patients. The issue is of course more complicated than that. Although reintervention rates and freedom from reintervention is often quoted in the literature it doesn't really give a true story of the relative experiences of the patients. The need for any reintervention is, of course, undesirable however there is a substantial difference between someone undergoing a conversion to open repair after EVAR when compared with a diagnostic mesenteric angiogram performed under local anaesthetic as a day case, for example. If a criterion were that only patients requiring or prolonging their initial hospital stay of >24 hours were considered to have a 'significant' reintervention then in this study; 28% of EVAR patients, 0% of fEVAR patients and 8% of OR patients required a 'significant' reintervention. ( $p=0.021$ ). It would be important in any future study of outcomes of endovascular (or open) repair of abdominal aortic aneurysms to assess the rate of 'significant' reintervention as well as all reintervention, to give a richer picture of the experiences of patients undergoing the operation so that judgements can be made regarding the true magnitude of the detrimental effect of reintervention.

Those undergoing standard EVAR will experience the need for more reinterventions and specifically more 'significant' reinterventions than those undergoing fEVAR or OR. However, there is no clear evidence that fEVAR confers the greatest advantage of all the repair types in terms of reintervention rates.

### **10.1.9. Conversion to Open Repair**

There was no statistically significant difference between the fEVAR and EVAR groups in terms of the number of patients requiring conversion to open repair. Three patients required conversion during follow up in the EVAR group and no patient experienced this particular complication in the fEVAR group. Common to all patients that required open conversion was that the maximum neck diameter in each case was greater than 32mm. Although it is difficult to draw firm conclusions from this small number of patients this may highlight this as a potentially 'more important' area of IFU violation than some others. There were only six patients in total that breached the IFU for neck diameter in the EVAR group meaning that half of all the standard stent-grafts implanted within a neck greater than 32mm required conversion to open repair.

### **10.1.10. Major Complications**

As discussed within the results section major complications seen during the primary hospital admission were not significantly different across the three treatment groups. However, what is striking is that a significant proportion (49%) of major complications seen in the OR group were related to intraoperative blood transfusion alone. This was also the category of complication with the largest single contribution to the overall total of major complications in any repair group. The reporting standards used to define the threshold for what determines a major complication in terms of intraoperative blood transfusion are primarily reporting standards for endovascular repair, although there are definitions relating to open repair contained within them also. It is reasonable to compare intraoperative blood transfusion in a like-for-like manner between endovascular and open repair as the physiological insult derived as a result of the need for blood transfusion and the blood transfusion itself remains the same. The fact that endovascular repair usually requires less blood transfusion intraoperative than OR is a testament to the less invasive nature of the procedure and one of a set of parameters that have helped to define the

theoretical advantage of the endovascular approach. However, the term major complication implies a clinically significant event that results in a risk of death for the patient or at least a prolonged disability of some sort. In fact, the reporting standards define a major complication as one that “indicates the need for significant intervention, prolongation of hospitalization more than 24 hours, and at most, minor permanent disability that does not preclude normal daily activity” at its least severe and “necessitates major surgical or medical intervention, may be associated with prolonged convalescence, is usually accompanied by prolonged or permanent disability, and may result in death” at its most. The reporting standards go on to give specific instructions as to how intraoperative blood transfusion should be assessed in terms of whether it is a mild, moderate or severe complication. The concern is that the threshold that is set for moderate or severe intraoperative blood transfusion is actually quite low. Any patient receiving the levels of blood transfusion intraoperatively as described for a moderate complication (>2 units autologous but < 3 units homologous) would almost certainly not result in a prolonged disability. Although the data collected and presented cannot answer the question of whether intraoperative blood transfusion prolongs hospital stay it seems unlikely that someone who receives 2-3 units of blood transfusion would be significantly impaired as to delay their discharge from hospital after an open aneurysm repair. In fact there was no significant difference in length of stay when comparing those patients who had a moderate or severe complication relating to intraoperative blood transfusion during OR with those who had no or mild complications relating to blood transfusion ( $p = 0.556$ , t test). Therefore, although it is not unreasonable to record intraoperative blood transfusion as a complication, and it is not unfair to compare OR and endovascular methods directly in this regard, what is not reasonable is the thresholds that have been set by the reporting standards. Any future research into this area should carefully scrutinise reporting standards with regard to what would constitute a major complication before commencement of the

data collection. Particular attention should be paid to the comparison between endovascular and open repair to give an accurate reflection of clinical consequences from this complication.

The recording and reporting of major complications gives an important insight into any medical treatment. It is not only important, so the patient understands what can potentially go wrong and therefore give truly informed consent but also, so the physician and patient can come to an 'educated' decision together as to what is the 'best' treatment option for them. To fully understand the 'risk profile' of the three treatment options however it is not adequate to consider only major complications on its own. As well as major complications, clinical failure (as defined within the reporting standards[93]), maintenance of device integrity and re-interventions are considered together below and collectively termed adverse clinical events (ACE). This is because any one of these may promote re-intervention, re-hospitalisation and/or death and by considering these together a deeper insight into how the three treatment options perform will be gained. It is important to still consider these elements separately as was done in the results section but to give a more patient centred and holistic view of the outcomes this type of interrogation is necessary. It is likely that patients consider 'problems' that are related to an operation together and do not in fact delineate between a major complication and a failure of the device but rather they will view all such things as 'problems' arising from the operation. It should be noted that they will however categorise and grade these 'problems' and assign different levels of importance depending on the individual 'problem' and its consequences for the individual patient. For simplicity however, the collective ACE are described here (excluding 'moderate' blood transfusion intraoperative as described above). For the EVAR group 16 patients suffered 29 ACE. In the fEVAR group 1 patient suffered 1 ACE and in the OR group, 15 patients suffered 26 ACE. The difference in the number of patients experiencing ACE reached statistical significance across all three repair groups ( $p= 0.007$ ,  $\chi^2$

test). In fact, fEVAR patients suffered significantly less ACE when compared with EVAR or OR groups independently ( $p= 0.002$  and  $0.015$  respectively,  $\chi^2$  test). Therefore, when looking at combined adverse clinical events fEVAR does confer an advantage over the other repair options.

#### **10.1.11. Summary of Primary and Secondary Outcome Measures Discussion**

With regards to the primary and secondary outcome measures there does not appear to be any advantage in performing fEVAR over all other types of repair and therefore the null hypothesis (fEVAR has the same clinical outcome as EVAR and OR for non-standard AAAs) cannot be rejected. The analysis does however reveal that there appears to be a disadvantage in performing standard EVAR in this group of patients. Namely that patients who received EVAR had a lower rate of primary technical success and importantly, an increased rate of clinical failure. Therefore, concerning the stated primary and secondary outcome measures EVAR appears to be the most inferior type of repair. Although not an outcome measure stated within the study the analysis of ACE provides an interesting insight into the overall experience of patients undergoing the three types of repair. This analysis suggests there is a specific advantage in performing fEVAR, however it would need further study with ACE as a specific outcome measure before this could be definitively stated.

## **10.2. Aneurysm Morphology**

### **10.2.1. Measurement of Aneurysm Morphology**

Prior to deciding on the measurement protocol used the chief investigator searched the literature and did not find a comprehensive protocol to describe validated measuring techniques across a range of anatomical variables. There were some reports and studies of isolated anatomical features but no comprehensive reports at the time when the study was designed (early 2012). Since then there has been a published report by Ghatwary et.al.

[196] in which a comprehensive measuring protocol is proposed - the St George's Vascular Institute Protocol. This was reviewed and in comparison to the protocol described in the methods section used in this study there are some important differences and also some similarities. It should be noted that the fact the measurement protocol used in the above study was not validated and do differ from those in the validated St Georges protocol (and other validated techniques for single anatomical measurements) there is limited application of the results of the above study because of this. The fact that the protocol used was not validated does not automatically and necessarily mean it was inaccurate or inferior but just that the results should be interpreted with this in mind. The first difference noted between the St George's protocol and the protocol used in this study are that Ghatwary et.al. propose the use of an automated central luminal line (CLL) and stretched vessel view for all measurements. Whereas in the protocol utilised in this study the CLL was manually imagined and created without automatic help from the software at all and stretched vessel view was not used. In both these instances it was specifically intended that way in order to preserve the 3-dimensional anatomy when making measurements and assessments. This is so the reviewer could continually utilise all the anatomical information available when making measurement-based decisions. Also, to the knowledge of the author, there has never been a comparison between the use of an automated or semi-automated CLL and a manually imagined one. Therefore, it is not known which method produces more accurate and reliable measures. The next prime difference was that the St Georges protocol was more substantial and expansive for both the aneurysm as a whole and the neck of the aneurysm itself. There were 13 different measurements for the proximal aortic neck alone in the St Georges protocol. This included volume and area measurements as well which was not included in this study. The parameters measured in this study were not designed to give an accurate overall assessment of the anatomy of each aneurysm but to determine whether it was 'inside' or 'outside' IFU and since the IFU used

doesn't include these other values there was no reason to include them. Although full anatomical assessment is important and useful for clinical decision making and research it was not the primary aim in this study. That protocol also measured neck diameter at 1mm intervals rather than 5mm intervals as was done in this study.

The St Georges protocol does not define where the top of the aneurysm begins and is inferior in this regard. Ghatwary et. al. show that: *“Better reproducibility in length measurements was achieved when using predefined anatomical landmarks, such as “the lowest renal artery to the aortic bifurcation” (RC 5 2.5%–4.2%), as opposed to more poorly defined areas such as “the beginning of the aneurysm sac” (RC 5 7.5%–9%).”*

This has been previously shown in other studies also [197]. The measurement technique applied in the St George's protocol for angulation was adapted from that published previously [198]. It describes a specific method to interrogate a 3 – dimensional model of the aneurysm to determine the maximum angulation for both the alpha and beta angles. The prescriptive nature of the description on how to do this would undoubtedly increase reliability and repeatability of such a measuring technique, as demonstrated by Van Keulen et. al. themselves. However, it is interesting that the ST George's team, when applying this method found the inter and intraobserver variability was less favourable than reported by the original Van Keulen study. Ghatwary et. al. also cite that they included more patients in their analysis lending more weight to their conclusion than Van Keulen et.al. Therefore, although the prescriptive nature of the measurement technique seems attractive it isn't necessarily the most repeatable way of measuring angulation. In reality it is difficult to find a practical and robust way of measuring angulation due to its complex 3-dimensional nature in an aneurysm. In this study this problem was mitigated by being prescriptive about the placement of where the vertex of the angle should be along the CLL. Something which Van Keulen et al. were not as prescriptive about. However, the potential limitations of the

method of angulation used in this study include the fact that angulation was measured along an imagined central luminal line rather than one created by the software. This would potentially increase the risk of measurement error for this particular measurement compared with other techniques. Also, it was not specifically stated to observe the area of interest rotated around 360 degrees though this was the intention. Without being prescriptive about this in the measurement protocol it is possible this was not always done and again may have led to inaccurate recording of an angulation that was less than the maximal actually present in the aneurysm being measured. Future methodologies for angulation measurement should be prescriptive as Van Keulen was about observing the aneurysm through a full 360-degree rotation using 3D software before deciding which view produced the maximum angulation. One addition to this though is that the protocol in this study required the reviewer to measure the angulation in 2 different planes which could potentially increase the accuracy of angulation measurement compared to the measurement of one angle. Of course, further research would be needed to clarify that but future methodologies for angulation measurement could include 2 separate measurements at least to ensure maximal angulation was recorded. Inevitably with both methods (Van Keulen and that presented in this study) there was an element of subjectivity but potentially a better way to reduce this even further would be to combine both methods. This would be an area for further and ongoing research.

Therefore, with regards to the measurement protocol the results of this study certainly do need to be analysed with the fact that a validated protocol was not used. This does limit the applicability and validity of the results however in the absence of a robust and continually well performing protocol the one used seems reasonable and at least was practical and relatively quick to apply. The design of the measurement protocol was in small part influenced by the desire to create a protocol which was not too time consuming

to apply, both in order to reduce the amount of time spent on it during the research but also with an eye on it potentially being applied in the clinical setting.

Two reviewers independently assessed aneurysm morphology to decide whether patients met the inclusion criteria and therefore could be classified as non-standard aneurysms or not. Regarding the agreement as to whether a patient exhibited a non-standard aneurysm or not the strength of agreement between the two reviewers was judged to be 'very good' as measured by Cohen's  $\kappa$  (0.969 (95% CI, 0.928 to 1),  $p < 0.0001$ ). This method of identification of patients will reduce potential bias compared to one reviewer assessing each scan on their own, however it is true there is still the potential for error to be made in the decision as to whether a patient had a non-standard aneurysm or not. Using defined anatomical criteria for the inclusion of patients along with a prescriptive method of measuring certain anatomical characteristics such as the alpha and beta angles was invoked to try to reduce this potential bias further. It would have been possible to carry out a parallel study to ascertain the inter and intra-observer variance to identify the degree to which the measurements produced by the two reviewers varied but it was deemed not necessary to carry out such an analysis. Firstly, when considering if patients were to be included or not it did not matter whether the measurements observed were different and to what degree, what mattered was the final decision whether they were non-standard or not. Secondly there is previously published data on inter and intra-observer variance relating to measurements from CTA and it was felt not necessary to repeat this. That study showed a minimal and acceptable rate of variance.[199]

Once a patient was included in the study the pre-operative CT scan was reviewed again to document measurements of anatomical criteria by the chief investigator. Here there is again potential for measurement error. The use of prescriptive methods of measuring each anatomical criterion, ensuring that all the CT scans were reviewed using the same

workstation and reconstruction software and that when viewing the images, they were all pre-set to defined window width (800) and window level (100) helped to reduce potential measurement error.

### **10.2.2. Consideration of Patients with Complex Iliac Anatomy**

When assessing patients for inclusion into the study only anatomical characteristics pertaining to the neck of the aneurysm were used to define whether an aneurysm was 'non-standard' or not. This is despite the fact that all manufacturers of stent-grafts have similarly strict criteria, set out in the indications for use, pertaining to the iliac vessels. This was a deliberate choice for three main reasons.

1. It was important to capture patients that best represent the clinical dilemma that a surgeon faces that is at the heart of this study: for patients with aneurysms that are not suitable for standard EVAR, what is the best method of repair in terms of clinical outcomes? The most common reason that a patient is not suitable for standard EVAR is anatomical characteristics that pertain to the aneurysm neck.[117, 200]. Aneurysms that violate the IFU because of anatomical characteristics pertaining to the iliac vessels present a distinct and different problem, that can be overcome using different techniques other than fenestrated technology. In fact, with hindsight, the hypothesis could have been more prescriptive in its wording to help define the intended patient cohort as non-standard aneurysms in which fEVAR would be a valid alternative treatment option to standard EVAR or OR. Rather than simply all patients who are not suitable for standard EVAR.
2. Breach of IFU from an iliac anatomy point of view alone does not influence whether fenestrated stent-graft technology needs to be used to seal more proximally. Therefore, if patients were included in the study based on being outside

IFU concerning iliac anatomy then there would potentially have been a subset of patients that had 'standard' necks being compared to other patients with a 'non-standard' neck. Specifically, complications secondary to failure mechanisms that are related to device failure at the proximal neck would have been compared for one group treated inside the IFU and one outside the IFU. This would have resulted in a small group of patients – 'inside IFU neck, outside IFU iliacs' and if included in the 'standard EVAR' group could have potentially biased the results for that group. However, it is possible that patients who were outside IFU for the iliac segment were included in the study but not identified as such as no measurements of the iliac segment were recorded. What is not known is whether these patients were preferentially selected for one type of repair over another and it is feasible and possible that a proportion of patients that underwent open repair as opposed to endovascular repair did so primarily based on their iliac anatomy. This again could have potentially influenced outcomes of patients, as being outside IFU for iliac anatomy implies more challenging anatomy overall, and the corollary of this is a more difficult operation, whatever the method of repair chosen.

3. The construction of a fenestrated stent-graft differs from that of a standard endovascular stent-graft primarily at the 'top end' of the device, that which seals in the neck. Challenging neck anatomy was the primary reason for development of fenestrated technology in the first place. This was so that the seal zone could be moved proximally, away from disease or unsuitable necks. The configuration of the device that seals in the iliac vessels is the same in both devices.

Therefore, there is a potential confounding factor (complex iliac anatomy) that is present but unmeasured in the study population. As stated, it is unusual for an aneurysm to be deemed unsuitable for standard EVAR because of iliac anatomy alone and therefore any unmeasured bias in this regard is likely to have a limited effect on the results. In future

study however, it would be important to address this issue by measuring iliac anatomy so its effects on the outcomes of aneurysm repair could be analysed and taken into consideration.

### 10.2.3. Consideration of Thrombus and Calcification within the Neck

Regarding specific anatomical characteristics measured on the pre-operative CT scan there were broadly two types of anatomical characteristics that were measured: Firstly, objective measurements were made of neck length, neck diameter (both at the maximum diameter and how the diameter changed over the length of the neck for 15mm), the  $\alpha$  and  $\beta$  angles and the maximum aneurysm diameter. The amount of thrombus within the aneurysm neck was also measured. The second type of measurement made was a more subjective measurement of the amount of calcification within the aneurysm neck. The IFU recommendations for the three manufacturers used to design this study vary regarding thrombus:

- Endurant Stent Graft System (Medtronic, Inc. Minneapolis, Minnesota, U.S.A.) - no mention of thrombus within the IFU
- Gore Excluder AAA Endoprosthesis (W.L. Gore & Associates, Inc. Flagstaff, Arizona, U.S.A.) - IFU comments that the device should not be placed where there is 'significant thrombus' but gives no definition as to what would constitute significant.
- Zenith Flex AAA Endovascular Graft (Cook Medical, Bloomington, Indiana, U.S.A.) - IFU states that significant thrombus, as defined as >2mm in thickness or covering  $\geq$  25% circumference of the aneurysm neck would be considered outside of the indications for use.

To enable the most objective assessment as possible of thrombus within the aneurysm neck the definition within the Zenith IFU was used when measuring thrombus within the neck for all aneurysms to ascertain if they fell outside the IFU or not. As it so happens in all of the standard EVAR the Zenith platform stent-graft was implanted.

Calcification was graded as; not present, mild, moderate or severe for each aneurysm studied. Although there is inherent subjectivity in this method of measuring and recording calcification there was no simple or reliable way that the extent of calcification could be measured objectively. This is in part due to the fact that although thrombus tends to form in a crescent shape along the inner surface of the aneurysm neck calcification is much more sporadic and varied with 'lumps' of calcification present at different points along the neck and round the circumference of the neck. In addition, thrombus is an intraluminal entity whereas calcification is present within the wall of the artery. This means that although two patients may have a similar burden of calcification in terms of volume, they may not deform the circumferential shape of the neck to the same degree. This circumferential deformity probably causes the most deleterious effects on the sealing of any endovascular repair within the neck. Therefore, the grading of calcification was in fact grading of the severity of deformation of the neck secondary to calcification, rather than volume of calcification alone. When the presence or absence of calcification was compared across all three groups there was no statistically significant difference found. In addition, not one case was included in the study solely due to the presence of calcification. This suggests that either calcification was not present to a significant degree in the population studied or that it had little bearing as to which type of repair they were selected for. These facts, along with the subjective nature of its measurement, dictated the decision not to consider the presence of calcification as a violation of IFU for the purposes of the further analysis.

There were no statistically significant differences in the amount of thrombus or calcification observed in patients across the three groups. However, the results show that those patients undergoing EVAR exhibited more infrarenal thrombus than either the fEVAR or OR groups. This finding is hard to explain but may be an indicator as to the general arterial health of the population selected for EVAR rather than a specific choice to treat these patients preferentially with EVAR. Thrombus within the infrarenal neck would generally be present in those with arteries of inferior quality and if this is a surrogate marker for the general health of the patient then might explain why these patients underwent endovascular repair as opposed to OR. However, when comparing both those with significant thrombus who underwent EVAR and those without there is no apparent differences in the pre-operative history to suggest that these patients are less fit. The median ASA grade in both groups was 3, the number of patients who had previous myocardial infarction or symptomatic ischaemic heart disease were higher in the no thrombus group (24% vs 17%). It is therefore difficult to explain this difference in presence of thrombus across the three repair groups. In light of the worse long-term outcomes after EVAR regarding renal function it would be important to investigate this area further in any future study as increased thrombus burden within the neck could potentially shed light on the aetiology of this complication due to the potential for thromboembolism into the renal arteries during aneurysm repair.

#### **10.2.4. Aneurysm Diameter**

The maximum aneurysm diameter was smaller, but not significantly so, in the group that received fEVAR (Median 60mm, Range 57 – 64). The reasons for this are unclear but the result could be a type I error, due to the small number of patients in the fEVAR group. In fact, the larger study of 107 patients who underwent fEVAR (detailed in chapter 8) showed the maximum aneurysm diameter to be closer to that of both the EVAR and OR groups in this study (Median 64mm, Range 55 - 92). It is unlikely that patients who had smaller

aneurysms were preferentially selected for fEVAR. What is possible however, and more likely, is that patients with very large aneurysms were preferentially selected for either standard EVAR or OR. This is because there is a delay of between 8-12 weeks present with fEVAR from the time of decision to operate to operation date that is not present with the other repair options. This time delay is to allow manufacture and delivery of the bespoke device to take place. It is feasible that a surgeon faced with a very large aneurysm at significant risk of rupture would not wish to burden the patient with an extra 3 month wait during which time they would be exposed to a risk of rupture when there is no delay (in theory) if another repair method is chosen. In fact, there was only one aneurysm (7%) with a maximum diameter of 70mm or more repaired in the fEVAR group whereas there were seven (24%) in the EVAR group and 13 (35%) in the OR group.

#### **10.2.5. Neck Length**

The aneurysm neck was significantly different between the groups. They were longer for patients who received EVAR compared with the other two repair groups. This is perhaps unsurprising as neck length would be the primary and most obvious determinant of whether a patient would be 'suitable' for standard EVAR or not. Of all the anatomical measurements made when assessing what type of repair a patient can be offered safely neck length is one of the simplest and most obvious measurements to make. It is also one of the anatomical measurements in which there is a significant amount of data from the literature to suggest inferior results in standard EVAR when placed outside the IFU for neck length [68, 104]. It is therefore unsurprising that neck length is significantly longer in this group with only seven (24%) patients exhibiting a neck length outside IFU for standard EVAR. When comparing the group with a neck length outside the IFU for standard EVAR (< 15mm) with those that were within the IFU there were no significant differences seen in the rates of complications as outlined below:

*Table 10.3 Comparing those Within and Outside IFU for Neck Length in EVAR Group*

Complication	Short neck (<15mm) (n=6)	Long neck (≥ 15mm) (n=22)
<b>Major Complications (In hospital), n (%)</b>		
Yes	0	4 (18)
No	6 (100)	18 (82)
<b>Migration (≥ 5mm), n (%)</b>		
Yes	3 (50)	6 (27)
No	43(50)	16 (73)
<b>Neck Effacement, n (%)</b>		
Yes	2 (33)	1 (5)
No	4 (67)	21 (95)
<b>Endoleak (Any), n (%)</b>		
Yes	4 (67)	6 (27)
No	2 (33)	16 (73)
<b>Endoleak (Graft Related), n (%)</b>		
Yes	1 (17)	2 (9)
No	5 (83)	20 (91)
<b>Open Conversion, n (%)</b>		
Yes	1 (17)	2 (9)
No	5 (83)	20 (91)
<b>Major Complications (Long term), n (%)</b>		
Yes	3 (50)	10 (45)
No	3 (50)	12 (55)
<b>Clinical Failure, n (%)</b>		
Yes	3 (50)	8 (36)
No	3 (50)	14 (64)

Table 10.3 - Comparison of categorical variables was performed using Fisher's exact test (†).

Neck effacement is a term that describes progressive cephalad progression of the aneurysmal process following endovascular repair. It acts to reduce the length of seal

within the decreasing aneurysm neck even if there is no migration of the stent-graft. Its aetiology is probably of continued aneurysmal progression rather than secondary to the repair itself but there is no study in this area. It is important to note in this situation specifically as effacement in a neck that is already short in which a standard EVAR is placed outside of IFU could quickly result in complete loss of seal, type 1a endoleak and consequently repressurise the aneurysm. In both patients who exhibited neck effacement with short necks no graft related endoleak was seen during the follow up and their aneurysms were noted to be shrinking. In the one patient with a long neck (22mm) their aneurysm was noted to be expanding with migration of the stent graft during follow up but no endoleak was seen on any surveillance imaging. With small numbers of patients exhibiting effacement it is difficult to ascertain the consequence or importance of this particular complication in this study but what is suggested by these results is that a long neck pre-operatively doesn't necessarily protect against effacement occurring.

The neck diameter was also less in the group who underwent standard EVAR. This would be expected given the findings relating to neck length. In both the fEVAR and OR groups there were a significant proportion of patients recorded as having no infrarenal neck whatsoever, five (33%) in the fEVAR group and eight (22%) in the OR group. This means that the aneurysm was present immediately below the renal arteries and therefore by definition, in these patients, there was a larger neck diameter below the renal arteries where the measurements were made.

#### **10.2.6. Angulation**

The  $\alpha$  angle was significantly greater in patients who received OR compared with those that underwent fEVAR, however there were no statistically significant difference between the two endovascular methods of repair. This may highlight that when a surgeon is faced with an aneurysm with significant angulation within the visceral aorta, they would be less

inclined to use an endovascular method of repair. This is unsurprising given that angulation may preclude or render endovascular repair more challenging whereas angulation would be of less concern when carrying out OR, and certainly wouldn't compromise the end result of the repair per se, in the same way.

The value of angulation as a predictor of clinical outcome was not seen in this study. By univariate logistic modelling alpha and beta angulation were assessed against the outcomes of technical success, reintervention (both perioperative and through FU), mortality (both perioperative and through FU) and clinical failure. These outcomes were interrogated and no statistically significant association was found. The literature examined did not shed any light on the value of alpha angulation as a predictor of outcome for EVAR, fEVAR or OR patients. The vast majority of studies don't analyse or measure it at all and primarily focus on beta angulation. The most important study identified in this regard is that by Hobo et.al. [67] a large study from the EUROSTAR registry. In that study that compared <60 degrees of beta angulation with >60, they found that greater neck angulation was associated with an increased risk of migration perioperatively, type 1a endoleak and a predictor of late reintervention. This study therefore suggests the importance of beta angulation as a marker of clinical outcomes and the importance of analysing it as an anatomical variable for research and when evaluating a patient's anatomy for whether a stent-graft should be placed or not.

Standardised measurement of angulation as described in this study or that by Van Keulen et.al. is important for future research into the question of whether angulation as an individual characteristic is an important predictor of poor outcomes for NSA patients when comparing different treatment options. Although Hobo et.al. showed worse outcomes for >60 degrees compared to <60 degrees undergoing standard EVAR the question still remains whether the outcomes for patients with angulation outside the IFU translate to worse

clinical outcomes for fEVAR, EVAR and OR patients equally. Furthermore, it is the recommendation of this author that in all future studies alpha angulation should be measured, recorded and analysed when evaluating the impact of anatomical factors on clinical outcomes as the data with regards to this variable is lacking within the literature and it would be important to know the role that angulation at this level plays in outcomes for these three treatment options. This is especially because fEVAR potentially is the most negatively affected by alpha angulation as it is the one treatment of the three that requires accurate placement, manipulation and deployment within this area of the aorta.

#### **10.2.7. Consideration of Number of IFU Violations per case**

Patients who received standard EVAR had less IFU violations pertaining to their aneurysm when compared with the other two groups (median of 2 vs 3). In fact, 43% of patients who received standard EVAR in this study had only one IFU violation, compared with 7% and 16% for fEVAR and OR respectively. Therefore, those patients who underwent EVAR exhibited 'simpler' aneurysm morphology compared to those that underwent fEVAR or OR, they had; longer necks with a smaller maximum neck diameter, and although they exhibited slightly more thrombus there were fewer IFU violations per patient. This revealed that those patients with more complex aneurysms were selected for either OR or fEVAR preferentially which is unsurprising given the reported advantages of these types of repair over EVAR in these patients. These results suggest there is in fact two groups of patients being studied here and that future research should clarify this point in more detail before comparisons can be drawn. One group comprises patients with 'simpler' aneurysms that are borderline in terms of suitability for EVAR and that the other group of patients with distinctly more 'complex' aneurysms. These results suggest, importantly, that although patients who receive EVAR exhibit 'simpler' aneurysms overall, they still tended to have worse clinical outcomes. Therefore, it seems that the fine line of EVAR suitability is one that should be adhered to as, even with simpler aneurysms, they still had worse outcomes. If

aneurysms that are more complex have more favourable outcomes with fEVAR and OR it stands to reason that the simpler aneurysms would also have more favourable outcomes, potentially to an even greater degree. This therefore informs us that if an aneurysm is outside the IFU for standard EVAR they probably should not receive standard EVAR if possible. Unfortunately, however the current distinction still does not answer the question of whether these patients are better served with fEVAR or OR.

#### **10.2.8. Expected Clamp Site**

There was no statistically significant difference when comparing the level of expected clamp site across the three repair groups in terms of survival. Furthermore, there was no statistical difference across the three groups in terms of where the expected clamp site was according to pre-operative CT imaging. There were differences in the complexity of aneurysms treated across the three groups and therefore expected clamp site seems to be an insensitive predictor of aneurysm complexity.

Overall, the subjective assessment of where a clamp would be placed intraoperatively by reviewing the pre-operative CT scan has poor correlation with where the clamp was placed. Expected clamp site neither predicts outcome in terms of survival nor accurately reflects where a clamp would be placed were the patient to undergo an open repair. Therefore, there is little value in recording or assessing this variable in future research in an effort to try to compare patients who undergo OR with a specific level of clamp with those undergoing endovascular repairs. This highlights the difficulties when comparing these two, distinct treatment options and their inherent differences. It must be accepted that patients who undergo open repair may require any level of clamp intraoperatively regardless of what is assessed at the pre-operative CT scan. This should be borne in mind by the surgeon proposing OR to an individual patient, especially as higher levels of clamp site are associated with poorer outcomes[86], and the level of clamp site does not appear to be

able to be accurately predicted. Furthermore, it is suggested that clamp site as a definition of juxtarenal/suprarenal/non-standard aneurysms not be used in future research. The anatomical measurements described above should be used instead. The majority of studies identified within the systematic review evaluating open repair for NSA patients used a clamp placed above the renal arteries as a marker for juxtarenal aneurysm. However, in this study the definition of non-standard aneurysms identified a cohort of open repair patients in whom only 30% received an intraoperative clamp above one renal artery. Therefore, there is an important cohort of patients, identified by this research, that has so far been neglected within the medical literature. That is, patients undergoing open repair who are not suitable for standard EVAR but still can have an infrarenal clamp placed. This is an extremely important comparison to make as detailed in the design of this study. It also importantly limits the comparison that can be made from the systematic review presented in this thesis on open repair with the patients studied in the retrospective cohort studies as they seem to be anatomically distinct.

### **10.3. Operative data**

All cases in this cohort were performed in theatre under general anaesthetic. There is description, in the literature, of endovascular procedures being performed under regional or local anaesthetic as well.[201, 202] In this study the use of the operating theatre with general anaesthetic reflects local practice and resources specific to the centres studied rather than a distinct preference for these techniques over alternatives. It was impossible therefore to comment on the role these varying techniques may play in influencing the outcome from any given operation. This fact however is important to recognise; variation in the use of anaesthetic techniques or operating environment was not present in this study thereby reducing the number of potential confounding factors and allowing a more meaningful analysis with regard to the specific operation type alone. It is also possible to

perform OR through different operative approaches, namely either transperitoneal access (midline or transverse) or retroperitoneal access from an incision centred on the flank. There is some evidence that the retroperitoneal approach can improve outcomes for selected patients and may reduce pulmonary complications [203] but no patients in this study received OR via this approach and were all done transperitoneally, again reducing the risk of bias secondary to approach. From an endovascular point of view, it is also possible to access the arterial system percutaneously or via an open 'cut down' to the access artery. The proponents of the percutaneous approach suggest that it can reduce morbidity by reducing the invasiveness of the groin incision used and can reduce wound complications and recovery time; however, there has been little evidence of high quality in this area so far to show a true benefit with percutaneous EVAR [204]. All endovascular cases in this study received an open cut-down to access the arterial system with formal closure at the end. In two cases, a Rutherford-Morrison incision was used instead but these were for specific anatomical reasons identified pre-operatively. This again therefore eliminates potential bias that would have been invoked by differing approaches to arterial access. In fact, within the base site now all endovascular cases, including fEVAR are performed preferentially by percutaneous means.

The operation time was longer in the fEVAR group compared with both other groups with a median time of just over 5 hours compared with 3 ½ hours for EVAR and 4 hours for OR. This approached but did not reach statistical significance. The method used to estimate the operative time was open to potential inaccuracies, so the median time stated above may not be an accurate reflection of the true operative time; however, the same method was used regardless of the operation type so at least each group would be subject to the same inaccuracy. In order to estimate the operation time, the anaesthetic chart for the operation in question was scrutinised and the total time was estimated from that. The detail of recording on anaesthetic charts is variable and subject to differences between individual

anaesthetists who actually record the data. Occasionally but not often, the actual start of the operation or 'knife to skin' time would be recorded. When this was the case, this was taken as the true start time. On any anaesthetic chart there is inevitably a period of time where observations are recorded but the operation has not yet started. This is variable for each patient and operation type. Often this period of pre-operative recording is longer with OR simply because the anaesthetist will often place more invasive monitoring equipment such as arterial and central venous lines as well as cardiac output monitoring. This period of placing lines is not actually part of the true operation but will be monitored and recorded by the anaesthetist nonetheless. Despite this variable 'pre-operative' recording time, it is often possible to estimate the start of the operation as the patient's physiological parameters will often noticeably change at the start of the invasive surgical procedure and the intensiveness of the monitoring by the anaesthetist will increase and usually be duly recorded. This potential inaccuracy would generally lead to a longer operation time to be recorded than was actually performed for OR. Since the operation time was still found to be less than that for fEVAR this inaccuracy is unlikely to have significant consequences for these results. In essence we can be certain that fEVAR operations genuinely took the longest amount of time out of the three types of repairs despite inherent inaccuracies in recording data in a retrospective manner.

It is unsurprising that the operating time was found to be longest for fEVAR due to the complexities of that operation over EVAR and OR. It inevitably takes more time to accurately place and deploy a fenestrated stent-graft system due to the multiple target vessels that need to be identified, cannulated and secured with target vessel stents. It is interesting to note though that despite the burden of prolonged operating this does not seem to translate into worse outcomes in terms of immediate or delayed complications, prolonged hospital stay or increased use of blood transfusion. Although cost implications were not considered in this study the fact that fEVAR took longer to perform would

inevitably influence the cost to the healthcare system of this type of operation over the other two. fEVAR is already more expensive than either of the other two operations in terms of the cost of the 'consumables' used within the operation, namely the device itself, costing approximately £16,700 on average (range £12,000 - £30,000; The unit cost per device varies in line with the complexity of the bespoke stent-graft). This is in comparison with £6000 for a standard device and £100 for an OR graft. These lengthy operations therefore will only add to this high cost as operating theatre time is one of the most expensive periods of a patients care. Further research should take into consideration the cost of different types of operations, including the length of operations and even the total time spent in the operating theatre and not just the actual operation. As it is this value that will affect the overall total cost of an operation for an individual patient.

Unfortunately, a high proportion (65%) of patients did not have an estimate of intraoperative blood loss recorded. This proportion was higher in both the endovascular repair groups compared with the OR group. This is most likely due to:

- 1) It is not routine to record intraoperative blood loss within the clinical case notes. This is especially true when the procedure in question proceeded as expected with acceptable or minimum levels of blood loss as determined by the anaesthetic and surgical teams.
- 2) Endovascular operations typically do not result in the same level of blood loss as the more traditional open operation as one would expect. Therefore, the anaesthetic and surgical team may not feel it necessary to document the estimated blood loss when it was a minimal amount, for example <100mls.

For any given case, the lack of a recording of the intraoperative blood loss would indicate that for that particular patient there probably was a minimal amount of blood loss. This may not be true in every case but is a reasonable supposition. It is somewhat unsurprising

that OR patients received the highest volume of blood transfusion both autologous and homologous as the inherent invasive nature of this operation would inevitably result in a higher volume of blood loss. There was at least one patient within the open repair group who suffered significant morbidity and potentially mortality related to their significant blood loss, which could have potentially been avoided if they were able to undergo endovascular repair. The patient in question was estimated to have lost 3000ml of blood intraoperative and was transfused 1500mls of autologous blood and 500mls of homologous blood. During the first postoperative day their clotting profile was noted to be severely deranged with a concomitant anaemia. They died within the first 24 hours after the operation. This specific patient however was deemed not suitable for either endovascular approach due to angulation and tortuosity within the aneurysm neck as well as the fact that the target vessels did not have enough separation to allow satisfactory placement of a fenestrated device. It is possible that this degree of anatomical complexity is what lead to the difficulties and high blood loss. This case highlights the potential risk undertaken with open operation but also that in some circumstances this is the only therapeutic approach available to the surgeon and the patient. It also raises an interesting point with regards to the validity of this current research; the aim, as stated earlier, was to compare a group of anatomically homogenous patients to see which operation gave the best clinical outcomes. The idea was simple in that if by defining the patient cohort using anatomy derived from IFU then a group of patients that could potentially have undergone any of the three operations would be compared. This patient highlights the flaw in that design.

By using the criteria of IFU anatomy the inclusion of patients is limited to those out with IFU but does not limit solely to those with anatomy suitable for endovascular repair. This gives rise to the situation, as alluded to earlier, where we are comparing patients who underwent open repair (and it was either unfeasible or even technically impossible to place an endovascular device) with patients in whom received an endovascular device. Further

research should focus to determine outcomes for patients who would be suitable for all three repair types. Although this research gives an important insight into outcomes for these operations for all comers and indeed it seems to suggest that standard EVAR may not be the most suitable the question of whether open repair or fEVAR provides the best clinical outcomes is still to be resolved. There are different ways that future research could provide this answer and attention should be paid to the design of any future study with this problem in mind.

#### **10.4. Stent Graft Configuration**

In all cases of fenestrated EVAR the Zenith Fenestrated (Cook Inc. Bloomington, Indiana) platform was used. In the EVAR group, all patients received a stent-graft from the Zenith Flex (Cook Inc. Bloomington, Indiana) platform. During the period studied there was only one commercially available fenestrated device available, explaining why all the patients received this device. Regarding standard EVAR there were more devices available and in use during the study period, and all but one identified by this study was the Zenith flex device. The other being an aorfix stent graft. This patient was initially included as was the original design and intention of the study but after analysis and further statistical advice it was decided that excluding this one outlier in terms of manufacturer would give greater reliability to the results when assessing outcomes for Zenith devices. This is in acknowledgment that there is potential statistical bias invoked by the change of methodology after the beginning of data collection and analysis. It should be noted that initial analyses did not demonstrate different results in terms of primary and secondary outcome measures because of the fact that the aorfix patient was taken out of analysis. The fact that all of the patients received the Zenith flex device represents physician preference for this device overall. Using the institutional database for the Royal Liverpool University Hospital (the largest contributor of patients into this study) 143 patients

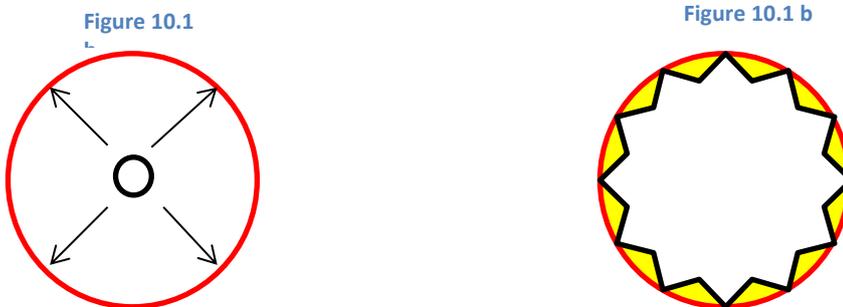
received standard EVAR over the period studied. Of these, 127 (89%) received a Zenith flex device, ten patients received a Gore Excluder device, two received an Aorfix device and in four no device was recorded on the database. All patients included in the retrospective multicentre and single centre studies above were identified from the above database. Simply put the physicians using these devices were more familiar with the Zenith flex and tended to place this device in all patients more frequently, as a consequence of this when faced with a patient with particularly difficult anatomy they would be more inclined to use a device that was familiar to them. Furthermore, the Zenith flex device has a perceived advantage over the Gore Excluder device especially in the setting of patients with complex neck anatomy - it possesses suprarenal fixation (uncovered metal barbs that extend beyond the upper part of the fabric) with the intention of providing extra fixation in the aorta adjacent to and above the renal arteries. The Gore device also has active fixation properties, but these are at the top of the fabric and hence are intended to act upon the infrarenal aorta.

#### **10.4.1. Standard EVAR**

When planning and deploying standard EVAR the manufacturers of all stent graft devices recommend that the proximal body diameter of the stent-graft be 'oversized' with respect to the neck diameter by 10 – 20%. There is evidence to suggest the radial force of the stent graft providing the effective seal is increased as the oversize is increased to 20%.[205] This is to provide additional radial force within the sealing zone of the stent graft within the infrarenal neck. Too small an oversize theoretically increases the chance of device failure by either promoting migration of the stent-graft caudally or by providing insufficient seal so that graft related endoleaks (Type 1a) occur. Too much oversizing can result in inadequate seal leading to type 1a endoleaks. This occurs because when the device is deployed from a constrained fashion to its full extent (as determined by the metallic stent) the fabric may

not fully expand as it cannot reach its full diameter, limited by the aortic wall. This leaves 'gutters' round its circumference through which an endoleak can occur. (See figure 10.1)

**Figure 10.1 Schematic Representation of Deployment of Oversized Stent-graft**



**Figure 10.1 a and b. Schematic representation of cross section of aorta (Red circle) and stent graft (Black), before deployment (Figure 1a) and after deployment (Figure 1b) if stent graft oversized too much. Gutters (Yellow shaded area) can act as channel for blood flow**

Analysing the data for EVAR patients within this study shows that a significant proportion of patients were out with this 'ideal' zone of 10-20% oversizing. When comparing the maximum neck diameter recorded for the infrarenal neck with the proximal main graft body diameter the following table details the oversizing used for the patients in the EVAR group (there was one patient in which the proximal body diameter was not available) (See table 10.4).

**Table 10.4. Amount of Oversizing in EVAR Patients**

Amount of oversizing	Number of patients (%)
<0%	2 (7%)
0 -10%	10 (37%)
10 – 20%	12 (44%)
>20%	3 (11%)

As can be seen from the table there were actually two patients in whom the proximal body diameter was less than that of the maximal neck diameter. The first case of 'under sizing' was in a patient with a maximum neck diameter of 34mm in whom a proximal main body of 30mm was implanted. In this patient, the neck diameter only dilated to 34mm at 15mm

from the lowest renal artery origin (LRAO). Above this, the neck diameter was 23mm at 5mm and 29mm at 10mm from the LRAO. Obviously, this constitutes quite severe conicality in this neck and presumably the intention was to try and provide seal within the upper portion of the neck albeit in hostile neck anatomy. In the other patient that was 'undersized' a stent graft with a proximal body diameter of 28mm was placed in a neck with a maximal diameter of 30mm. Again, the maximal neck diameter was only reached 15mm below the LRAO. Above this the neck diameter immediately below, 5mm and 10mm from the LRAO was 26mm. This again explains the choice of a 28mm diameter main body diameter; the purpose undoubtedly would have been to seal within the first 10mm of neck. Regarding the 10 patients who exhibited oversizing of between 0 and 10% all followed the same pattern as described above with the maximal neck diameter being reached 15mm from the LRAO. Of the three patients who had oversizing of >20%; one patient was oversized 21% and one 23%. These parameters fall within the realms of interobserver measurement error between the initial planning physician and the researcher within this study. Furthermore, it is unlikely that such a small amount of oversizing over the recommended threshold would have deleterious clinical consequences. There was however, one patient in whom the main stent-graft body used was 28mm representing a 33% oversize. This patient had a long (25mm) neck that was conical enlarging from 17mm proximally to 21mm at 15mm distal from the LRAO. There is no obvious explanation why this size of stent-graft was selected over a smaller one from the data collected, but there are many factors that may promote a clinician to choose a larger stent graft.

Although the above is interesting it is important to note whether any of the sizing discrepancies resulted in poorer outcomes for the patients. This was not specifically investigated during this study. As mentioned, there was one patient in whom no information was available regarding the size of the stent graft but in the remaining 27 patients there were 10 cases of clinical failure; 8 due to migration (with or without

subsequent open conversion) and two patients who died during their index admission. Of those eight patients with migration; five had oversizing <10% and three had oversizing of 10 – 20%. Both patients who were ‘undersized’ exhibited migration during follow up. Although the numbers are small in this study and no firm conclusions can be made regarding the amount of oversizing and the resultant clinical outcomes the results do suggest that it may play a role. The fact that a significant proportion of patients undergoing EVAR had stent grafts oversized <10% or >20% suggests that in this group of patients, those outside of IFU for EVAR pose a particular problem during the planning of the repair. Although the anatomy seen in this group is somewhat less severe than that seen for either the OR or fEVAR groups this is nonetheless an area in which fEVAR and OR have an immediate advantage as planning the amount of oversizing within a diseased infrarenal neck is not even done for fEVAR or OR as it is not necessary. This highlights the difficulties in providing this form of repair for patients who are outside IFU for standard EVAR and potentially represents another mode of failure for patients that would not be present if they undergo one of the other two types of repair.

### **10.5. Post-operative Outcomes**

A significant reduction was seen in the length of critical care stay and hospital stay overall for those patients who underwent repair by one of the two endovascular methods. This is unsurprising given the less invasive nature and lower inpatient complication rate seen in both these types of repair. This fact has obvious implications with regard to overall cost of the inpatient episode, but also will undoubtedly have an impact on the wider costs to the community and society once the patient leaves hospital. It is reasonable to assume that those patients who have a shorter in hospital stay with less complication will be more likely to return to full functional capacity similar to their pre-operative status and furthermore will be quicker to return to maximum functional capacity once they leave the hospital. This

means that the burden on community health and social services will be reduced in this population when compared with those undergoing OR. What is uncertain is whether this cost benefit does truly exist and if so, is it significant enough to make a difference to the overall cost. Previous studies have shown standard EVAR to be more expensive when compared with OR with the UK EVAR 1 Trial showing an estimated increased cost of EVAR in the region of £1000 for the inpatient episode and £3500 over the lifetime of the patient.[64] However, this analysis is over a decade old now, and compares standard EVAR with OR for patients with standard aneurysms, the applicability of these estimates to current practice with regards to non-standard aneurysms is therefore limited.

Although not possible to assess in this retrospective study another important consideration for any patient deciding about which operation to have would be the quality of life they can expect after the operation. This has been considered in randomised controlled trials comparing standard EVAR with OR and they found that scores for quality of life questionnaires are worse for OR within the first month after operation but return to pre-operative levels with either no difference or a slight benefit for those having undergone OR after 12 months. [64, 88]

## **10.6. Comparison of Standard with Non-Standard Aneurysms**

As standard aneurysms by definition did not undergo fEVAR comparison was only possible for EVAR and OR patients. This comparison was also limited by small numbers of patients identified especially for open repair. This makes meaningful comparison between these groups difficult. This should be borne in mind when analysing those results. The fact that the standard aneurysm patients were only identified from a single centre contributed to the confounding factors affecting the comparison of these groups. The differing nature of the open operation between standard and non-standard aneurysms is also a confounding factor – the fact that no patients received a clamp above the renal arteries in the standard

OR group compared to 30% of the non-standard group is an important point for note when comparing the outcomes. Very limited information can be drawn from the comparison between standard and non-standard patients because of the above considerations. Furthermore, the groups were heterogenous in terms of gender make up with more males predominating in the standard aneurysm patients. The standard anatomy patients were also significantly more likely to have a preoperative diagnosis of ischaemic heart disease and conversely non-standard patients had a significantly worse preoperative fEV1. Furthermore, and by definition the anatomical characteristics of the groups differed with significant differences in terms of neck length, diameter, alpha and beta angulation. Importantly however AAA diameter was similar between the two groups. Furthermore, the only significant difference found was that of primary technical success for open repair – meaning that open repair was more likely be technically successful regardless of whether the aneurysm was non-standard or not. This means that technical success across these three repair groups is primarily affected by whether it is repaired by open surgery or not - regardless of whether it is a non-standard aneurysm or not. It was also not possible to investigate the outcomes of mid-term survival and clinical success by the prescribed methods set out prior to analysis. This again highlights the need for statistical input prior to constructing a study design and methodology to enable this issue to be highlighted early so a solution can be found to it.

The rationale for the above comparison was to try and ascertain whether the distinction of anatomy between standard and non-standard was an important determinant of outcome however it is not possible, from the results presented to definitively state this one way or the other. From the systematic review conducted into outcomes for patients undergoing EVAR for NSA it appears, as stated, that the outcomes are worse. However, it could be argued that it is irrelevant whether the outcome for non-standard aneurysms are inferior to those of standard aneurysms. The anatomy of a patient is predetermined and non-

modifiable and therefore it is less important whether these patients have different outcomes compared to each other but what is important is whether a patient with a specific anatomy has different outcomes based on the treatment options available to them.

## **10.7. Summary of Discussion**

This study has failed to prove or disprove the hypothesis as set out in the beginning and the prime reasons for its failure to do so will be discussed in the next chapter. It has however revealed some important aspects regarding the treatment of patients with non-standard aneurysms. Firstly, EVAR has a lower rate of immediate technical success than either of the other two treatment options and over the longer-term patients have an increased rate of clinical failure compared to their fenestrated and open repair counterparts. This is all in the context of 'simpler' aneurysms anatomically. However, it should be noted that the findings of a statistical difference for technical success in this study are independent of whether the aneurysm is standard or non-standard and seem to be related to whether a patient has open repair or not. As discussed, this is likely due to the peculiarity of the definition of primary technical success in the reporting standards. These findings suggest that placing standard EVAR outside IFU is a 'bridge too far' for this technology and that where possible this method of treatment should be avoided. Patients who underwent OR showed an increased length of critical care and total hospital stay. Finally, fEVAR demonstrated the lowest rate of adverse clinical events (ACE) during follow up. The evidence does not state that fEVAR is the best treatment option for non-standard aneurysms but does suggest that it may be the least inferior option. Further study is needed to ascertain the true difference between these treatment strategies.

## 11. CHAPTER 11 - Discussion on Limitations and Design of Study

The design of any research study involves many aspects so that the study can proceed with a sound methodological and ethical grounding. One aspect of good study design should consider the practical issues of conducting the research with the resources available. Included in this is the time available to conduct and complete the research.

At the beginning of any research and central to all that follows should be the research question. This should be a clearly defined question from which a hypothesis can be drawn, and should be so from before the beginning of the research. After this a significant amount of groundwork needs to be done before the research actually begins and unfortunately this can often take a significant amount of time, putting pressure on an already constrained timeframe. Once the research question has been defined there are three important aspects that need to be satisfied before data collection and analysis can begin.

The first domain is with regards to methodology of the proposed study and its design. The most appropriate study design (i.e. randomised-controlled trial, case-control cohort study etc) should be chosen with clear reasons as to why this design was chosen over others. The selected design of study should then be interrogated intellectually to ensure it will provide a robust enough framework to enable the researcher to try and answer the question at hand with acceptable certainty. Ideally someone with expertise in the design of studies should be involved at this stage.

The second domain relates to the statistics used within a study. Ideally a statistician experienced in the area of research should be involved from the beginning and included when deciding on the study design itself. The type of statistical analysis to be used in the study should be set out from the beginning with the study question in clear focus at all

times. To enable meaningful statistical analysis consideration should be given to the number of subjects to be included in the research to minimise the possibility of error during statistical analysis.

The third domain relates to governance and ethics. All studies require an appropriate governance framework and within medical research those involving patients certainly require consideration of the ethics pertaining to the study and require ethical approval at a local, regional or national level, possibly all.

Supplementary to the above considerations the practicalities of how a study will be conducted also need careful thought and planning prior to the commencement of a study. These practicalities may also influence the above considerations – for example it may not be possible to conduct a randomised controlled trial to answer a particular question given the resources available.

This research was conducted as part of a higher degree by the chief investigator within a tertiary vascular unit at a teaching hospital (Royal Liverpool University Hospital) and was affiliated to the local university (University of Liverpool). There were no additional resources available such as research personnel. During the course of the research valuable lessons were learned about study design and the design of research projects within the above context. The chief investigator began the research post immediately following a clinical post and was a relative novice to the world of academia. There was a clear research question at the beginning which allowed the research process to begin in earnest. From there discussion and thought was given to the methodology of the proposed research and it was decided early on that the study would need to be in the form of a retrospective observational study. It was recognised that a prospective longitudinal study could most likely answer the question more accurately of whether fEVAR has the best clinical outcome as a treatment strategy for non-standard AAAs. However, there were important aspects

that were unknown about fEVAR, the alternative treatment strategies and more so non-standard AAAs that meant a retrospective analysis would give important insight and information that would help the design of a future prospective study. Furthermore, it was clear that it would not be possible to complete a prospective research project within the confines of a higher degree, mainly because the clinical outcomes that are of interest can take years to manifest and therefore a long follow up time would be needed. At this point the process of application for ethics approval and registering of the research study with local and national governance bodies began. It was decided that to obtain sufficient numbers of patients and to improve the validity of the research patients from other hospitals within the local region would be included. To lawfully obtain access to their health records approval needed to be sought to allow breach of confidentiality for research purposes. At the time this meant a further application to the National Information Governance Board (NIGB) for section 251 approval. The whole process of application and registration took approximately 6 - 9 months before final approval was granted to allow data collection to proceed.

With regard to the first domain mentioned above of design and methodology this study began strongly with a clear research question in focus and a defined set of outcome measures identified. This design and methodology were interrogated to some degree but then the study proceeded without logical analysis of the potential pitfalls. If the researcher had taken more time and consideration over these potential pitfalls it may have been improved. For example, if the study was designed to allow more flexibility then the methodology could have been optimised near the beginning when it became apparent there were fewer patients available for analysis than expected. In retrospect, a relatively likely complication that could have been foreseen. With regards to the statistical aspects of the study a statistician was involved in the final analysis of data however a statistician was not involved from the beginning and had no input at the design stage of the study. With

regards to the governance and ethical aspects within the study all requirements were fulfilled as early as practically possible but without adequately assessing the impact of trying to collect data from other centres it is likely that a large proportion of time spent on this area (gaining NIGB section 251 approval) was wasted as very little benefit in terms of numbers of patients was derived from this effort.

### **11.1. Limitation in Number of Patients**

The main limitation in this research was the final number of patients studied. The design of the study tried to mitigate this potential problem in two ways – to include patients operated on over a two-year period rather than one and to include patients treated at different hospitals within the local region. Initially it was decided to include patients operated on over the period of one year, but it became apparent that this would not return enough patients, so the time period was extended to two years. It was felt that to study more than two years would result in too onerous a task in terms of reviewing all CT scans and therefore two years was chosen as the appropriate compromise in this area. The researcher was mindful that a long follow up time would be needed to try and detect important clinical outcomes which occur over the longer term, this limited the most recent date a patient could have undergone their operation to 2008 (giving, at the beginning of the research project, a 4-5 year follow up time for the most recent patients). It was also noted that the introduction of the electronic storage of radiological images on the picture archive and communication system (PACS) began in 2006 and therefore it would be more difficult to obtain pre-operative CT scans prior to this time. As the introduction of PACS began in 2006 it was likely that there would be some difficulty in obtaining pre-operative images during this year, but it was felt the number would be relatively small. Unfortunately, it was not foreseen that there were significant difficulties in obtaining pre-operative CT scans performed during 2006 and the research was well underway by the time

this was identified. This unfortunately limited the number of patients with an available CT scan to scrutinise to identify if the patient could be included or not – 167 patients out of an initial number of 497 (34%) did not have a CT scan available for review. Although it is unlikely that all of these 167 patients would have met the inclusion criteria a significant proportion may have merited inclusion. Of those with a CT scan that was reviewed 59% had a non-standard aneurysm. Therefore, if the same proportion of patients with no CT scan met the inclusion criteria this would have brought the total number of patients studied to 180, more than doubling the number of studied patients. In retrospect it would have been prudent to assess the availability of CT scans prior to the main data collection so that a decision could have been taken at the time whether to shift the time period of interest one year later, with the acknowledgment this would sacrifice one year of follow up. This was a complication that could have potentially been avoided with careful thought and preliminary investigation into the practicalities of obtaining CT scans.

In order to increase the number of patients available for study and to widen the scope of the study to a multicentre trial it was decided to include patients operated on at different sites across the region of Cheshire and Merseyside. The decision to include patients operated on at other sites was deliberately made to try and increase the number of patients but also to try and improve the validity of the results when applying them to a general vascular population with AAA. This is because the Royal Liverpool University Hospital, the base site where the research was carried out, is a tertiary referral centre specialising in complex aneurysm repair including fEVAR. The valid concern was that the population being studied would represent an unusually complex group of patients and therefore the results would only be applicable to a similar group of complex patients. The decision was made to include patients from other centres and this therefore necessitated the application to NIGB to seek section 251 approval. This application process was lengthy as already stated – meaning that data collection from the other sites to be included in the

study began months after data collection from the base site. Out of the original 7 sites planned to be included in the study no patients could be identified from four of the sites. In each case, initial contact was made through coding departments, theatre departments or individual vascular surgeons. In each case the problem was either that relevant CT scans could not be transferred as there was no longer a copy of the preoperative CT scan available or a list of patients was unable to be provided. This latter problem was despite the researcher and supervisor contacting the personnel at each hospital and visiting the sites to meet with relevant personnel. Simply put: requests were made for lists of patients for potential inclusion into the study but there was no response to the request. After more than a year of trying to obtain lists of patients it was decided to abandon trying to get patients from these centres as the researcher was nearing the end of his time in a dedicated research position and the data collection had almost been completed with the already included patients. The pragmatic decision was taken to complete the research with the limited number of patients already obtained. During the period of research, the vascular services within the Cheshire and Merseyside were undergoing major reconfiguration as part of a national programme of service reconfiguration within vascular surgery. One of the sites traditionally part of the Cheshire and Merseyside region merged with a vascular centre in another region. Three sites (Arrowe Park Hospital, Countess of Chester Hospital and Warrington Hospital) were in the process of merging during the research period. The other three sites (Royal Liverpool University Hospital, Aintree University Hospital and Southport Hospital) became fully integrated during the period of research. Due to the relocation of vascular services from some hospitals there was no permanent vascular presence at the majority of the sites left and this undoubtedly made lines of communication more difficult. There was no permanent staff member who could help to take things forward 'on the ground' when there were issues. Furthermore, individual surgeons who had initially agreed to help with data collection inevitably became

busy with the agenda of reorganisation and therefore were unable to devote time to help with the research project. In total, 11 patients were identified from other centres that were finally included for analysis. One patient was from Southport hospital and the other 10 from Aintree hospital, from both these hospitals there were no significant delays or difficulties in obtaining a list of patients for potential inclusion into the study. Therefore, the final result of trying to include patients from sites additional to these two lead to over a year delay in the finishing of data collection and analysis with no additional patients finally included. It is difficult to see how one could have envisaged the degree of difficulty encountered in this area at the outset, however some preliminary background work may have helped. It would have been possible to use two or three sites as test sites and if initial lines of enquiry received no response or revealed that only small numbers of patients would be accessible to review then it could have been decided to abandon this plan. With the realisation that trying to include patients from other sites would have been too costly in terms of time utilised with very little benefit in terms of numbers of patients. The time saved in this aspect could potentially have been used to extend the base hospital search to three years instead of two for example. Although this problem encountered is specific to this research it does highlight the difficulties of carrying out research across multiple sites from one centre with no dedicated research personnel or even 'points of contact' at spoke sites. For future study into this area it would be recommended to conduct a multicentre trial – but recruit research personnel at each site to help drive forward data collection and potentially even analysis. A collaborative effort would greatly increase the productivity of such a study. Furthermore, it would be beneficial to choose at least one other site that also perform complex aneurysm repair and fEVAR as well as at least two other sites that perform OR and EVAR. This would ensure sufficient numbers of patients studied that underwent fEVAR as well as maintaining the generalisability of the results to all

Given the poor yield of patients from hospitals in the surrounding region as was the original intention of the study it is important to characterise and define the patient population that was captured. Of the final 80 patients that were included: All 15 patients who underwent fEVAR were from the Royal Liverpool University Hospital, all 28 patients who underwent EVAR were from the Royal Liverpool University Hospital and the majority of patients (26 patients) undergoing open repair were treated at the Royal Liverpool University Hospital. Ten patients undergoing open repair were treated at Aintree University Hospital and one was treated at Southport hospital. Therefore, the majority of these patients and all of the endovascular cohort were from a single centre. Although this study was multicentre region wide in its design, in actual fact after patient capture it essentially was a single centre retrospective study. It should be noted that the Royal Liverpool University Hospital is a tertiary or quaternary referral centre and receives referrals and operates on patients that are referred from other regions. Aintree University Hospital is a similarly sized teaching hospital within Liverpool (5 miles apart) and therefore it is reasonable to assume that the patient populations captured by both hospitals are similar in terms of demographic detail. This fact therefore limits the applicability of the results to a wider population of patients presenting to a district general hospital for example, or in a different part of the country. This is unfortunate as the original intention within the design of the study was to enable comparison of results with most other unselected populations including patients presenting to a district general hospital.

It is also noteworthy that of the final 137 CT scans reviewed more patients were deemed non-standard (81) than standard (54) – in 2 patients there was disagreement between reviewers. This result suggests a potential sampling bias inherent in the design of the study as it would normally be assumed that the majority of patients treated for aneurysmal disease are within the IFU for standard EVAR. As stated above this probably reflects the fact that the majority of patients were identified from the Royal Liverpool University Hospital

which as an expert referral centre will inevitably receive a disproportionate number of non-standard aneurysms. This was an important reason that the initial study design aimed to capture a region wide population to try and mitigate this type of sampling bias. Furthermore, it is possible that within the large proportion of patients without a CT scan (167) there would have been a significant number of standard aneurysms that have been missed by this study. Numerous studies from the systematic review into outcomes after EVAR for non-standard aneurysms (Chapter 5) however did show that in their patient populations more patients had a non-standard aneurysm compared with standard. Of course, these studies will be limited and biased by the same factors mentioned above but it is noteworthy that a similar discrepancy is seen among other studies. Ten studies specifically compared outcomes between non-standard and standard aneurysms and of those four reported a larger number of non-standard aneurysms than standard in their study [95, 96, 102, 106, 116]. In fact, from all ten studies the number of non-standard patients was 1377 (46%) and standard patient was 1634 (54%). Therefore, it may not be that there was a significant sampling bias at all, but that assumptions that the vast majority of aneurysms treated have standard anatomy is wrong. Of course, as stated this may just be true for tertiary referral expert centres but nonetheless would be an important area for future research – to determine the proportion of nonstandard aneurysms treated (by any method) within a population of aneurysm patients.

## **11.2. Limitation with Definition of Non-Standard**

Another limitation with the study was that by using the inclusion criteria of ‘outside IFU for standard EVAR’ led to a number of patients being included that were not suitable for either fEVAR or EVAR. This means that the population being studied is not as homogenous as one would desire. In order to address this problem, there are many ways in which a study could be designed. The first and probably most obvious is to design a randomised controlled trial.

This would allow prospective analysis of all cases and only those that were felt suitable for an endovascular repair would inherently be included into the study. The other obvious advantage of an RCT would be to eliminate selection bias as was present in the current study. The disadvantage of this design of trial is that it would be both expensive and time consuming. Furthermore, there is some evidence to suggest there is a perioperative mortality benefit in patients undergoing fEVAR compared with OR [170] which raises an ethical question of whether it would be appropriate to propose a trial where patients would be randomly allocated to an operation which may in fact incur a greater perioperative mortality. In fact, with the removal of selection bias the perioperative mortality rate for those undergoing OR that would be seen may be even higher. It would of course be possible to design an RCT where patients in whom there was clinical equipoise as to the 'best' treatment option would be randomised to a treatment and in those in whom there was no equipoise they would go on to receive the prescribed treatment but under the auspices and follow up of the ongoing trial. In practice however such a trial may be difficult to implement in a standardised way as inevitably there would have to be a subjective assessment at some point by an individual as to whether a case represented equipoise or not. To circumvent the ethical dilemma offered by an RCT a well-designed prospective study in which patients were assessed at the outset and only included if they were technically suitable to undergo either fEVAR or OR would answer the question adequately. The surgical team, along with the patient, would retain the right to make an informed choice of which operation to have and with appropriate pre-operative assessment of the patients the selection bias could at least be quantified and taken into consideration within the analysis.

### 11.3. Comparison of Literature with Studies

Three systematic reviews were carried out as part of this thesis to give a background and to try and inform and help the discussion regarding outcomes for non-standard aneurysms. The first point of note is the significant heterogeneity between studies within each of the systematic reviews makes comparisons between those studies and the completed research potentially flawed. The majority of the literature also documents a time frame when significant technology advances were and still are being made. In endovascular surgery there appears to constantly be new innovation and at the time of writing there are currently devices available, with ancillary equipment, that can treat aneurysms with an infrarenal neck of 4mm or longer within IFU. Although this limits the applicability of results from this, past and similar studies for the future the majority of aneurysms treated are still within the anatomical variables defined within this study. More importantly the question of those patients who are 'borderline' for standard EVAR still present themselves in everyday clinical practice. The conclusions of the systematic reviews detail that patients with NSA who undergo standard EVAR experience an increased rate of type 1a endoleak both within 30 days from the index procedure and beyond when compared with SA patients. They also experience an increased risk of secondary intervention, usually to maintain proximal seal. There was however insufficient evidence to suggest whether these findings equate to significantly worse outcomes for NSA patients in terms of all cause or aneurysm related mortality beyond 30 days. With regard to NSA patients undergoing open repair the systematic review could only draw very limited conclusions due to the poor methodological quality of the studies and the heterogeneity evident between them. The systematic review of fEVAR for NSA patients identified that it has acceptable clinical outcomes both in the short and longer term. Again, there was however heterogeneity between studies published and especially when concerning comparative studies making valid comparison difficult.

Overall within the limitations of the literature and the above studies the clinical outcomes of the three treatment options are similar for non-standard aneurysms. The systematic reviews also highlight areas for recommendation with regard to reporting and further research: Long term data (beyond 5 years) is lacking for NSA patients undergoing standard EVAR and represents an area ripe for further research. It is recommended that future reports should analyse patients defined by anatomy relating to the IFU for the device implanted to allow comparisons of patients across a time period which has seen significant advances and evolution in technology. There is also a need for adherence to already published reporting standards for open aneurysm repair. At the least adherence to definitions regarding juxtarenal aneurysms should be adhered to, ideally future reports would adopt the definition of non-standard aneurysms as outlined in this thesis to allow meaningful comparisons of an anatomically homogenous population. Bearing in mind that clamp position in itself is not the sole definition of what makes an aneurysm non-standard. Furthermore, specific anatomical data should be published when reporting outcomes for fEVAR patients. It is important to know the potentially relevant role different anatomical characteristics play in the outcomes of patients undergoing one of these treatment options.

In order to ascertain if there was significant sampling bias invoked by the lack of patients identified for this study important demographic information was compared with the published literature presented in the systematic reviews also. This is especially because the vast majority of patients were treated at one centre, contrary to the intention and design of the study. Compared with the literature, NSA patients undergoing EVAR in this study tended to be older, but a similar proportion were male and for the studies in the literature that reported ASA grades the rates were similar. 81% ASA grade 3 or 4 in the current study, rates of between 50-100% in the literature. Pulmonary disease was poorly reported within the literature and the relative rates cannot be commented upon. Furthermore, baseline

size of aneurysm between the literature and the current study is similar. The fact that there is an increased perioperative mortality rate and poorer long-term survival rate within the study above compared with the literature for NSA patients undergoing EVAR is difficult to explain purely based on the comparison of demographic information. The most likely reason for these observed differences is that the current study is inaccurate due to the small number of patients included. This suggests limited information can be drawn from these results and therefore conclusion about comparisons to fEVAR and OR are further limited.

Regarding the fEVAR patients within the current study the age, AAA size and proportion of male patients was similar to the reported literature. Furthermore, with a mean of 3 target vessels per patient the complexity and demographic details were very similar to the reported literature. The main difference was that the ASA grade of patients in the current study was more commonly 3 or 4 (80%) compared with the literature which was less than 70% in the majority of studies that reported ASA. Despite these differences the principal outcomes were similar between the literature and the current study though again inference of treatment effect is limited due to the small number of patients in the current study, and for the reasons stated above comparisons with the EVAR cohort should be made only with caution. For open repair patients the most significant difference is that all patients within the literature identified had a clamp placed above at least one renal artery compared to 30% within the current study. This suggests a different anatomical cohort and as this study is primarily assessing outcomes and comparing them based on anatomical criteria comparison of results with the literature is likely to be flawed.

For the above reasons and the fact that the vast majority of patients identified were treated at one site the generalisability of the results of the above study to a wider population are impossible to make. It may be reasonable to compare the outcomes with

other tertiary referral centres with a similarly complex case mix, but this would need to take into account the specific definition of non-standard aneurysm.

#### **11.4. Limitation in Study Design/Methodology**

The common thread to the major difficulties encountered during this research study, outlined above, relate to a lack of forward planning/pilot research. In retrospect, initial investigation with a limited pilot study to determine numbers of patients available for review may have been beneficial. This should have been done prior to designing and planning the main study and may have led to not only greater efficiency but a larger number of subjects included within the study. This pilot study could even feasibly have been performed prior to the dedicated period of research further increasing the time available to the researcher to plan, design, and conduct the study. The pilot study could also have been engineered to collate data on simple, important outcome measures – such as mortality - this would have made sample size and power calculations possible in the design phase of the study. This, in turn, may have been able to influence decisions such as prolonging the study period to three years to try and capture more patients.

A statistician was not involved in the design of the study from the beginning and was only included after the commencement of data collection. In the beginning the statistics to be used were simple and mostly descriptive in nature, therefore it was felt that statistician involvement was not strictly necessary. As the study progressed more complex ideas of what may be possible with the collected data emerged – such as the possibility of generating models to predict risk in similar patient populations with non-standard aneurysms. At this point it became clear that for help with more sophisticated statistical techniques statistician involvement would be necessary. At that point data collection was well underway. Ideally a statistician would have been involved from the start, for several reasons. Firstly, statistician input would have been extremely helpful during the design

phase of the study and with their experience in study methodology, they may have been able to improve upon what had been planned. In this study there was no change to the way the data was analysed as set out prior to statistician involvement but agreeing upon statistical methods to analyse data at the start is important to avoid the possibility that analysis techniques are changed to better fit collected data.

In summary, this research could have been conducted more efficiently and potentially included more patients if the following things had been done differently:

- Once the research question had been identified and an outline of the main study design and methodology had been decided categorisation of potential problems and pitfalls would have been useful. Categorisation into methodological, statistical and governance issues would be useful. In addition to this a category of practical issues – such as whether CT scans would be available, whether patients will be able to be identified from other centres or not – may have improved this study.
- Once the relevant, main issues had been identified a focussed pilot study with strictly defined aims would have been extremely helpful. The aim of such a pilot study would be to address each of the problems outlined in the above phase and should therefore be strictly time limited to avoid it partially replacing the main study.
- Statistician involvement from the beginning – even at the stage of setting the pilot study.
- The process of governance and registration with various institutions (University, ethics committee, research department) to begin as soon as possible, potentially even before the beginning of the research post.

For future research it would be important to adhere to the above principles when beginning and conducting the research as much as possible. For any future prospective

study into this area the lessons learned within this study and detailed in this chapter could be considered as part of a pilot study and should help to inform the design of such a study.

### **11.5. Suggestion for Reporting Standards**

It is the recommendation of this thesis that the definition of non-standard aneurysm/anatomy used in this thesis should be adopted within the reporting standards. The term juxtarenal aneurysm should no longer be used. Suprarenal and thoracoabdominal aneurysms remain as acceptable definitions. Furthermore, all studies that report on aneurysm repair of any type should specifically state the proportion of aneurysms that are treated as NSA or SA and report their outcomes separately. This would allow true comparison of patients across studies and help the community to understand the possible inferior outcomes when treatment is out with the IFU for standard EVAR. To define non-standard as any aneurysm with anatomy outside the IFU for the stent-graft implanted. Anatomical detail should be given for the cohort about the proportions of patients that are out with the IFU for each anatomical characteristic, an overall number of IFU violations and a mean (+/- standard deviation) of IFU violations for the patient cohort to allow better comparisons. When a patient has not yet undergone standard EVAR or is due to undergo another method of repair non-standard aneurysm is defined as an aneurysm that is out with IFU for any standard device without ancillary equipment such as endoanchors. It is appreciated that ancillary equipment recognises a special circumstance and these patients should be analysed separately and as a separate treatment modality from standard EVAR. A 'standard' device is one that does not maintain flow to any visceral vessel by deliberate augmentation of manufacture of the device in a special way to create branches, fenestrations or scallops to maintain such flow. It is intended that the seal zone of the device is entirely below the visceral vessels. Chimney endovascular repair again is a

separate entity and should be analysed as such. Specific anatomic criteria are not defined to characterise a non-standard aneurysm primarily because it is envisaged that the IFU of standard stent-grafts may and will evolve with technological development and therefore setting a limit of 10mm for neck length, as an example, may potentially include people as non-standard now that in the future may be treated within IFU. Of course, analysis and review of any new device with different technology that proposes to treat anatomies currently outside of IFU is important to determine whether outcomes truly are no more inferior. However, if a device were to be introduced with similar outcomes and differing IFU an important advantage of the definition of non-standard, as stated, is that it takes this future development into account.

With regards to measurement of aneurysms a validated protocol such as that proposed by St Georges institute should be followed to provide reproducibility with the added caveat that the top of the aneurysm be clearly defined. In this study the definition used was that when the neck diameter increased by 10% from the lowest renal artery this was said to be the point at which the aneurysm began. However, it may be more appropriate to define the top of the aneurysm as the first point of infrarenal aorta that reaches 30mm in diameter regardless of what happens below that and even if it is 30mm at the level of the renal arteries. Furthermore, any aneurysm neck with a diameter of 36mm should be excluded and described as a type 4 or other thoracoabdominal aneurysm to separate these aneurysms from non-standard aneurysms, the anatomy of interest.

Non-standard aneurysms could be classed as either severe or less severe anatomy representing those patients with more severe IFU violations and those with less, however further work needs to be done to define which anatomical criteria play a greater and lesser role before deciding on such cut offs.

With regards to the measurement of renal function and its deterioration or lack thereof there are two points of note. Firstly, perioperative renal dysfunction (that seen within the first 30 days after the index operation should be defined as anyone suffering an acute kidney injury as per the definitions set out in the KDIGO definition. Furthermore, the stage of acute kidney injury (1,2 or 3) should be reported with the proportion of patients suffering no AKI, AKI stage 1, 2 and 3 in the results. In practice this will require measurement of the serum creatinine in the acute hospital stay. Furthermore, any patient requiring dialysis as an inpatient should be reported and whether this dialysis continued beyond discharge and was either a) permanent or b) was discontinued because of an improvement in native renal function. If dialysis was later stopped because of transplantation, then this should be made clear in the reporting of this outcome. Regarding chronic kidney disease measurement over the period of follow up it is recommended that eGFR be used as the surrogate marker for chronic kidney disease and comparison with pre-operative values is important. Again, the KDIGO definition and reporting of the category of chronic kidney disease is recommended. When presenting the proportion of renal deterioration over follow up the proportions of patients moving 'down' a category should be stated and whether anyone eventually requires dialysis for renal dysfunction. The use of these definitions for both acute kidney injury and chronic kidney disease are recommended by The Renal Association in the UK.

Regarding primary technical success it is recommended that future studies clearly state primary technical success as defined in the reporting standards. With specific attention paid to the fact that a graft related endoleak present on completion angiogram disqualifies the use of the term primary technical success. It is recognised that the majority of these endoleaks seal spontaneously and do not cause further deleterious sequelae and the term adjusted primary technical success can be used for such patients in whom the endoleak seals spontaneously without adjunctive manoeuvres. Authors should clearly state the

primary technical success and adjusted primary technical success rate, so it can be clearly seen that this factor has been investigated and taken into consideration.

Another suggestion is for the inclusion of a term “Adjusted clinical success” this could be used to identify those patients detailed as a clinical failure, appropriately by the reporting standards, that then ‘regain’ clinical success. This of course is a retrospective definition and can only be determined once a patient has completed follow up but nonetheless is an important factor to determine the clinical impact of certain modes of failure that are believed to lead to serious consequences. It is proposed that this is not always the case and the definition of adjusted clinical success helps to identify cohort of patients that don’t appear to have deleterious effects from clinical failure.

### **11.6. Future Study Design**

The specific lessons learned from this study that could be applied when designing any future prospective study into this area are outlined below:

- 1) Inclusion criteria – Pre-operative assessment by CTA would be mandatory. Only if a patient was out with the IFU for standard EVAR then should they be included. Furthermore, an assessment should be made to ascertain if a patient would be able to have fEVAR either within IFU or out with it. If so then the patient should be included.
- 2) Anatomical classification - A system of classifying the anatomical complexity would be more useful and should be more detailed and robust than the existing definition based on anatomy (Infrarenal, pararenal, juxtarenal). It should include important parameters such as neck length, diameter and conicality. As well as alpha angle measurements. Thrombus load and beta angle measurements should be made and recorded although it should be recognised these probably play a less important role than the variables mentioned above. In the current study only four patients

were outside the IFU solely related to thrombus load and one patient solely related to beta angle. The degree of calcification within the neck should not be included in any scoring system of anatomical complexity as calcification is a subjective measurement with no pre-defined criteria for its severity and furthermore as seen in this study never solely contributed to an aneurysm being considered outside of IFU. There are therefore four important domains of neck characteristic that would need to be included into any anatomical scoring system: 1) neck length and diameter 2) neck shape (conical or not) 3) Angulation 4) presence of thrombus. A formal assessment of iliac anatomy would be useful to ascertain whether there truly are patients that are turned down for endovascular repair solely due to unfavourable iliac anatomy or not. This anatomical scoring system could be used to help define or delineate what constitutes 'simple' non-standard AAA anatomy and what constitutes 'complex' non-standard anatomy.

- 3) Complications – The thresholds for what constitute a major complication should be rationalised and should reflect clinical practice. Furthermore, as experience with endovascular repair has grown a more mature understanding of the failure modes and mechanisms of stent-grafts has developed and this should be borne in mind when designing any study and particularly what data points should be captured to accurately reflect the incidence of adverse clinical events related to the aneurysm repair.
- 4) Technical success – particular attention should be paid to the recording and reporting of technical success, especially with regards to the evolution of the idea that some proximal endoleaks may seal spontaneously without adverse event and therefore do they truly represent technical failure?

- 5) Cost – As broad an interrogation of costs of differing treatments as is practically possible would be desirable. This would include not only inpatient costs but also costs when people are discharged from hospital
- 6) Quality of life measures – Further research should aim to clarify the position of previous studies, and confirm they hold true for patients with nonstandard aneurysms, that quality of life following open repair or endovascular repair is similar in the long term.
- 7) Choice of repair – Recording of reasons why a specific type of repair was chosen by surgeon and/or patient would be helpful to give a clearer picture as to the clinical context for each case.
- 8) Contrast use – as stated it would be important to record diligently variables which may explain some of the significant outcomes seen in this study – such as contrast use.
- 9) Pre-operative aneurysm related deaths – it would be important to identify any cases of aneurysm rupture while waiting for eventual repair to ascertain whether this plays an important role.

As stated within the results section the majority of patients included and all of the endovascular cohort were from a single centre. This was despite the fact the design of the study was such with the intention of capturing patients from an entire region and patients treated at district general hospitals as well as teaching hospitals. As stated, the applicability of the results to a wider population of patients presenting to a district general hospital for example, or in a different part of the country are limited. This is unfortunate as the original intention within the design of the study was to enable comparison of results with most other unselected populations including patients presenting to a district general hospital. However, the population of patients captured within the study is that presenting to an experienced high-volume centre treating these patients. Furthermore, many of the patients

were referred from locoregional hospitals and further afield. It is therefore reasonable to suggest that results seen for these patients would be applicable to another high-volume experienced centre receiving referrals from their own locoregional health care community. With the progression of reorganisation of vascular service within the United Kingdom to fewer, high volume centres the results from this research therefore become applicable to those centres routinely carrying out open or endovascular surgery for non-standard aneurysms. The original design to include district general hospitals may not be applicable anymore.

Further research would be useful however to ensure that the results seen in this study are not particular to the Cheshire and Merseyside Region. Local collaboration with expert units in other parts of the country would be needed to answer this problem and control for that particular confounding factor. In the first instance it would be relatively straight forward to set up a research partnership with similarly sized hospitals in the Greater Manchester region especially since these units already have close professional links. The other significant advantage of including hospitals further afield (i.e. Manchester) rather than just the one region would mean that patients treated by fEVAR would not be from one hospital and therefore applicability of results to the wider national population would be possible. Furthermore, numbers of complex endovascular cases would be greater allowing for more meaningful analysis.

## **12. CHAPTER 12 - Conclusion**

Although the hypothesis from this study cannot be accepted on the evidence presented by its findings it does give credence to the suggestion that fEVAR may indeed be the method of repair with the best clinical outcomes for non-standard aneurysms. However, with regards to the cohort being studied, patients who underwent standard EVAR have a significantly worse outcome after their aneurysm repair, as determined primarily by rates of clinical failure. This is despite the fact that the morphological features of aneurysms who went on to have standard EVAR tended to be less 'severe' than the anatomy of those patients that went to have OR or fEVAR. It can therefore be recommended from this study that where possible placement of standard EVAR devices out with IFU should be avoided in preference for an advanced stent-graft technique or open repair. Further study needs to ascertain the magnitude of any differences in clinical outcomes between OR and fEVAR.

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## **Appendix 1 – Full Search Strategy for Systematic Review of Clinical Outcomes Following Placement of Standard EVAR stent Graft in Non-Standard Anatomy**

- 1 Medline exp "AORTIC ANEURYSM, ABDOMINAL"/ 17045
- 2 Medline (juxtarenal OR pararenal).ti,ab 1201
- 3 Medline (aneurysm\*).ti,ab 108834
- 4 Medline (2 AND 3) 632
- 5 Medline (1 OR 4) 17265
- 6 Medline (Fenestrate\* OR Endovascular\*).ti,ab 43664
- 7 Medline (Repair\* OR Procedure\* OR Intervention\*).ti,ab 1964743
- 8 Medline (6 AND 7) 25247
- 9 Medline (fEVAR OR EVAR).ti,ab 3299
- 10 Medline (8 OR 9) 25501
- 11 Medline (Infrarenal OR hostile OR inadequate OR short OR IFU OR "instruction\* for use" OR "Indication\* for use" OR angulation OR diameter OR length).ti,ab 1470741
- 12 Medline (neck\*).ti,ab 188240
- 13 Medline (11 AND 12) 18036
- 14 Medline (5 AND 10 AND 13) 650
- 15 Medline 14 [DT 1998-2018] [Languages English] [Humans] 596
- 16 EMBASE exp "AORTIC ANEURYSM, ABDOMINAL"/ 1743
- 17 EMBASE (juxtarenal OR pararenal).ti,ab 1510
- 18 EMBASE (aneurysm\*).ti,ab 135056
- 19 EMBASE (17 AND 18) 862
- 20 EMBASE (16 OR 19) 0
- 21 EMBASE (Fenestrate\* OR Endovascular\*).ti,ab 63576
- 22 EMBASE (Repair\* OR Procedure\* OR Intervention\*).ti,ab 2638437
- 23 EMBASE (21 AND 22) 37614

24 EMBASE (fEVAR OR EVAR).ti,ab 4975

25 EMBASE (23 OR 24) 38205

26 EMBASE

(Infrarenal OR hostile OR inadequate OR short OR IFU OR "instruction\* for use" OR "Indication\* for use" OR angulation OR diameter OR length).ti,ab 1868886

27 EMBASE (neck\*).ti,ab 260695

28 EMBASE (26 AND 27) 26734

29 EMBASE (20 AND 25 AND 28) 207

30 EMBASE (16 OR 19) 2544

31 EMBASE (25 AND 28 AND 30) 207

32 EMBASE 31 [DT 1998-2018] [Languages English] [Humans] 185

## Appendix 2 – Full Search Strategy for Systematic Review of Clinical Outcomes Following Open Surgical Repair in Non- Standard Aneurysms

#	Database	Search term	Results
2	Medline	(juxtarenal OR pararenal).ti,ab	1211
3	Medline	((aneurysm* NOT intracrani*) NOT TEVAR).ti,ab	99935
4	Medline	(2 AND 3)	637
6	Medline	(Open).ti,ab	433206
7	Medline	(Repair* OR Procedure* OR Intervention* OR Surgery*).ti,ab	2712908
8	Medline	(6 AND 7)	113731
9	Medline	(4 AND 8)	252
10	Medline	9 [DT 1998-2018] [Languages English] [Humans]	221
11	EMBASE	(juxtarenal OR pararenal).ti,ab	1538
12	EMBASE	((aneurysm* NOT intracrani*) NOT TEVAR).ti,ab	117984
13	EMBASE	(11 AND 12)	865
14	EMBASE	(Open).ti,ab	554822
15	EMBASE	(Repair* OR Procedure* OR Intervention* OR Surgery*).ti,ab	3661613
16	EMBASE	(14 AND 15)	164665

17	EMBASE	(13 AND 16)	361
18	EMBASE	17 [DT 1998-2018] [Languages 313 English] [Humans]	

### Appendix 3 – Full Search Strategy for Systematic Review of Clinical outcomes Following Fenestrated Endovascular Aneurysm Repair fEVAR Systematic Review

#	Database	Search term	Results
1	Medline	exp "AORTIC ANEURYSM, ABDOMINAL"/	17221
2	Medline	(juxtarenal OR pararenal).ti,ab	1209
3	Medline	((aneurysm* NOT intracrani*) NOT TEVAR).ti,ab	99694
4	Medline	(2 OR 3)	100267
5	Medline	(1 OR 4)	102605
6	Medline	(Fenestrate*).ti,ab	3562
7	Medline	(Repair* OR Procedure* OR Intervention*).ti,ab	1979206
8	Medline	(6 AND 7)	1279
9	Medline	(fEVAR).ti,ab	120
10	Medline	(8 OR 9)	1286
11	Medline	(5 AND 10)	756
13	Medline	11 [DT 1998-2018] [Languages English] [Humans]	592
14	EMBASE	exp "AORTIC ANEURYSM, ABDOMINAL"/	1930
15	EMBASE	(juxtarenal OR pararenal).ti,ab	1521
16	EMBASE	(aneurysm* NOT intracrani*) NOT (TEVAR).ti,ab	155728

17	EMBASE	(15 OR 16)	156373
18	EMBASE	(14 OR 17)	156398
19	EMBASE	(Fenestrate*).ti,ab	4587
20	EMBASE	(Repair* OR Procedure* OR Intervention*).ti,ab	2660137
21	EMBASE	(19 AND 20)	1916
22	EMBASE	(fEVAR).ti,ab	173
23	EMBASE	(21 OR 22)	1928
24	EMBASE	(18 AND 23)	1104
25	EMBASE	24 [DT 1998-2018] [Languages English] [Humans]	973