A Risk-adjusted and Anatomically Stratified Cohort Comparison Study of Open Surgery, Endovascular Techniques and Medical Management for Juxtarenal Aortic Aneurysms:

The UK COMPlex AneurySm Study (UK-COMPASS).

Clinical Study Protocol

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Study Protocol Approval

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List of Abbreviations

AAA	Abdominal aortic aneurysm
A-DQol	Aneurysm – Dependant quality of life questionnaire
A-SRQ	Aneurysm – Symptom rating questionnaire
A-TSQ	Aneurysm – Treatment satisfaction questionnaire
BAR Score	British aneurysm repair Score
BEVAR	Branched endovascular aneurysm repair
CE	Conformité Européenne (Confirmity marking for European Economic Area)
CT	Computerised Tomography
DICOM	Digital Imaging and Communications in Medicine (standard for distributing and viewing medical image regardless of the origin)
DMEC	Data Monitoring and Ethics Committee
EQ-5D 5SL	Euroquol – Five dimension questionnaire
ETTAA	Effective treatments for thoracic aortic aneurysms (Study)
EVAR	Endovascular aneurysm repair
FEVAR	Fenestrated endovascular aneurysm repair
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment (programme of NIHR)
HQIP	Health Quality Improvement Partnership
ICER	Incremental cost effectiveness ratio
IEP	Internet exchange portal
IFU	Indications for use (sometimes referred to as 'Instructions for use')
NAAASP	National abdominal aortic aneurysm screening programme
NCAPOP	National clinical audit and patient outcomes programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NVR	National Vascular Registry
ONS	Office for National Statistics
OSR	Open surgical repair (of AAA)
PACS	Picture archiving and communications system
PMG	Programme management group
PPI	Public Patient Involvement
PROMS	Patient-reported outcome measures
RCT	Randomised controlled trial
SD	Standard deviation
SSC	Study Steering Committee
QoL	Quality of life
QUALY	Quality adjusted life years
TAR	Technology assessment report

Background and Rationale

Abdominal Aortic Aneurysms (AAAs) are common. There is a national screening programme involving an ultrasound scan for all men at age 65. Normally an AAA is considered for repair when it is 55 mm or larger in size. About 6,000 people per year undergo major elective surgery in the UK for AAA with the aim of preventing premature death from aneurysm rupture. The complexity of aneurysm surgery depends on the anatomical relationship of the aneurysm to the renal and other visceral arteries. The least complex AAAs to treat are "infrarenal" with a "neck" at least 10 - 15 mm in length below the renal arteries. When the AAA is closer to the renal arteries, it is called a juxtarenal AAA. Operations for juxtarenal AAA are more complex, hazardous and expensive compared to infrarenal AAA, because there is little or no neck on which to secure a graft. The main surgical strategies for AAA treatment are Open Surgical Repair (OSR) and EndoVascular Aneurysm Repair (EVAR) techniques.

Open surgical repair involves surgically replacing the AAA with a synthetic graft. This is very major surgery which causes severe physiological stress due to: 1) the extensive laparotomy required for access, 2) the consequences of aortic cross clamping, which causes cardiovascular instability, and 3) the systemic effects of lower torso and lower limb ischemia-reperfusion injury. Repair of juxtarenal AAAs may require a suprarenal or a supracoeliac aortic cross clamp, which causes additional renal and visceral ischemia-reperfusion, thus increasing the risk of organ failure and death. Postoperative mortality and morbidity rates are therefore significant, even among patients considered to be physiologically fit enough for such major surgery.

EVAR is a technique which is associated with potentially less physiological stress. It involves implantation of a stent-graft system within the AAA, bridging the normal segments of aorta above and below the aneurysm segment. Stent-grafts are introduced into aorta via the femoral arteries without a need for laparotomy and without aortic cross clamping. For an infrarenal AAA the stent-graft can be secured to the neck of the AAA below the renal arteries, provided that it is of suitable shape and quality. That is not the case for juxtarenal AAAs: they require specially designed stent-graft configurations, to enable fixation at renal artery level or above. These stent-grafts are provided with openings (fenestrations) to allow blood flow into visceral and renal branches of aorta (called 'target vessels'). Additional stent components are required to secure the fenestrations to the target vessels. This technique is called Fenestrated Endovascular Aneurysm Repair (FEVAR) and can be done wholly percutaneously, although many centres still use small cut-down incisions in the groins. The avoidance of laparotomy and aortic cross clamping renders this procedure physiologically less stressful to the patient, leading to quicker recovery and improved perioperative safety. This operation can also be performed under spinal anaesthesia without the need for general anaesthesia. It is therefore considered an especially attractive approach for patients who are at high risk or unsuitable for open surgical repair.

UK National Clinical Audit 2015 reported the observed postoperative mortality for juxtarenal AAA to be high at 18.6 % for OSR and 4.3 % for EVAR techniques, considerably higher than that for infarenal AAA of 3.2% for OSR and 0.8% for EVAR.

Although FEVAR has been specifically developed to treat juxtaranal AAA, other techniques are also utilised. These include off-label insertion of a standard stent-graft designed to repair infrarenal AAA (outside the conditions of manufacturers' Indications for Use (IFU) / licence). While there is evidence that such 'off-label standard EVAR' is associated with poor results in the short as well as the long

term, a number of opinion leaders have been advocating its use in some patients instead of FEVAR, on the basis of unproven value and the high cost of FEVAR. Off-label standard EVAR is used in a substantial proportion of patients but cannot be grouped together with FEVAR and must be considered separately.

Other operations for juxtarenal AAAs include novel techniques such as 'Chimney EVAR', which describes a technique of placing a stent-graft designed to treat infrarenal AAA deliberately over the renal and visceral arteries, while preserving the blood flow to them via stents placed running parallel to the fabric of the stent-graft. In this configuration the use of all of the implants is considered off-label. This technique is used in a few hospitals for a limited number of patients.

Despite the apparent advantages of endovascular techniques, including FEVAR, controversy persists about their role compared with open surgical repair, for two main reasons:

1) ***Long term survival***. Despite its lower perioperative mortality, endovascular repair is not expected to lead to improved survival in the long-term. This is because EVAR techniques including FEVAR are associated with a steady and life-long incidence of late complications, requiring secondary intervention, and which may ultimately lead to failure of the stent-grafts resulting in patients' death. In addition, the treatment population is elderly, usually with multiple co-morbidities, and successful AAA treatment has little effect on other causes of death.

2) ***Cost.*** FEVAR devices are expensive and their cost effectiveness is widely questioned, particularly because any potential incremental clinical benefit is not expected to reflect in a marked improvement in long-term survival.

Open Surgical Repair is also costly, largely on account of longer hospital stay and higher intensive care use when compared with infrarenal aneurysm repair.

No medical therapy can prevent aneurysm rupture. Medical management involves treating co-morbidities in order to optimise fitness of the individual adequately to allow aneurysm repair by one of the techniques mentioned above and/or to slow aneurysm expansion, since the risk of rupture increases with increasing size of AAA. When the risk of aneurysm rupture is considered to be smaller than the risk of death from an elective repair, a physician and their patient may wish to keep the surgical option available for the future, without imminent surgery, even if the aneurysm is larger than the recognised size 'threshold' of 55 mm. Such patients are observed with a view to offering surgical intervention when the perceived risk of rupture increases through aneurysm enlargement. This is referred to as 'Operation-deferred Medical Management' in this proposal.

Current clinical practice and commissioning would benefit greatly from evidence on how different treatment strategies for juxtarenal aneurysms compare: this is the remit of the HTA commissioned research call 15/153.

How does the existing literature support this research?

This research plan draws from existing literature in the following main areas:

1) HTA TAR: This is a comprehensive systematic review of comparative evidence for FEVAR *v* OSR. The report includes research priorities identified in this area.

2) An additional literature review of endovascular techniques not included in the TAR, but since recognised to be used as alternatives to FEVAR.

3) Reports from major RCTs in the area of EVAR in general to glean methodological aspects, including economic analyses.

1) HTA TAR:

The primary aim of the HTA Technology Assessment Review (HTA - 13/09/01) was to examine evidence comparing FEVAR with OSR for juxtarenal AAAs, as well as comparing branched-EVAR (BEVAR) with open repair for thoracoabdominal aneurysms. A total of 5,253 records were identified from bibliographic databases and conference proceedings. After de-duplication 3,268 records were screened at title and abstract stage and 24 publications were retrieved for full-paper screening. All 24 studies were excluded because none satisfied the predetermined inclusion criteria for satisfactory internal validity. Sixteen of these studies were excluded on study design, six were excluded on intervention and the remaining two were excluded on comparator. Among the 6 papers excluded on intervention, three did not specify that FEVAR was the endovascular technique, one used off-label standard EVAR only and the other two were reports of 'surgeon-modified' devices and not company-manufactured devices. Five out of 16 studies that were excluded on study design reported a comparison. For all of the studies, however, the authors acknowledged that they had allocated treatments selectively, that the different groups were not comparable at baseline, but that they had employed no method of accounting for the resulting bias. Therefore, none of these studies was considered to have satisfied the inclusion criteria.

2) Additional literature review:

We performed additional literature searches to cover a) papers published after the inclusion period of HTA TAR; and b) treatment of juxtarenal AAA with other endovascular techniques such as off-label standard EVAR and novel techniques such as 'chimney EVAR'.

We identified and screened 92 records at title and abstract stage, retrieved three publications for full text review and evaluated them against the same inclusion criteria as the HTA TAR. Again, none was eligible for inclusion due to a lack of demonstrable comparability of baseline anatomical and physiological characteristics between different cohorts. This was also the case with the multicentre (national) study from France that included a comparison of FEVAR against OSR for juxtarenal AAA. All three reports acknowledged selective allocation of treatment modality. At least two journal editorials have highlighted the shortcomings in reporting of the French multicentre study, with one of them suggesting that the overall results were unreliable due to poor performance of some centres (cluster effect). Furthermore, in the absence of long-term survival data or any QoL data, the report's conclusions regarding cost effectiveness remain unconvincing. Some authors concede that they compared OSR in low risk (fit) patients against FEVAR in high risk (unfit) patients, without including any method of adjusting for biases in their studies.

The main lesson to be learnt from the French study and the rest of the literature is that a robust method of accounting for confounding factors such as indication and risk biases is essential for a cohort comparison study in this area.

A review of the health economic literature is included in a later section describing our health economic analysis plans.

Evidence explaining why this research is needed now

The national aortic aneurysm screening programme has resulted in increased numbers of men being identified with AAAs at the age of 65: these are in addition to the substantial numbers of people whose AAAs are discovered incidentally. The capacity to offer treatment to avoid the risk of rupture, at relatively low risk, has increased greatly in the last 15 years as a result of EVAR. More recently, advances in the design of stent-grafts has meant that AAAs which are juxtarenal can be treated by EVAR using specially designed 'fenestrated' stent-grafts. These are costly, but their use needs to be balanced against major and high risk open surgery, or a decision to avoid treatment, with a continuing risk of aneurysm rupture.

During the last few years, these choices have resulted in very difficult decisions for vascular specialists and their patients, because there is little evidence comparing FEVAR and OSR, both in terms of their clinical outcomes and their cost implications. Of the last 50 FEVAR procedures done in the Chief Investigator's hospital, the mean cost of the FEVAR device alone was £ 16,724 (range £12,000 – 30,000) with an additional cost of £ 2,500 (range 2,000-4000) for ancillary implants. FEVAR procedures require numerous consumables (catheters, guidewires, balloons etc), and prolonged operating time in an endovascular ('hybrid') theatre that incorporates imaging equipment, by a multidisciplinary team, typically including two consultants. Lifelong surveillance imaging and a need for secondary interventions adds further to the costs. The alternative - open surgery - is a complex major procedure with a higher risk of morbidity and mortality, and is associated with intensive care costs and sometimes prolonged hospital stay.

Because of the very high costs of fenestrated stent-grafts, it has become common practice for vascular specialists to use stent-grafts designed for infrarenal AAAs outside the Indications For Use (IFU) to treat juxtarenal AAAs. This risks complications, a need for further procedures and the possibility of medicolegal consequences of 'off-label' use.

All UK arterial centres now provide an EVAR service and the use of FEVAR is increasing. Between its introduction into the UK in 2005 and December 2010, approximately 350 FEVAR procedures were done. By contrast a similar number are expected to be done during the current calendar year alone. This equates to an estimated NHS spend of £6.7 million (+VAT) on implants alone for UK FEVAR programme.

Uncertainty about when to use FEVAR, when to use open surgery, and whether to use infrarenal EVAR devices 'off-label' is currently a real dilemma for vascular surgeons and their patients and is a major source of concern for commissioners. Evidence is needed urgently to inform treatment choices for patients with juxtarenal AAAs. This study would provide the necessary data, based on contemporary UK practice.

Aims and Objectives

The aim of our proposal is to answer the research question identified by the NIHR HTA Commissioning Board: *What is the clinical and cost-effectiveness of strategies for the management of juxtarenal abdominal aortic aneurysm, including fenestrated endovascular repair?*

We plan to answer the above question in terms of research priorities identified within the HTA TAR, as well as the terms of the commissioning brief.

We have designed a cohort comparison study using routinely collected data from existing databases, namely, National Vascular Registry (NVR), Hospital Episode Statistics (HES); imaging reports and raw data from the NHS Picture Archiving and Communications System Internet Exchange Portal (PACS IEP); and directly collected data from arterial centres in England. Linkage of data from these sources will provide the comprehensive dataset required to achieve the following objectives in relation to patients with juxtarenal AAA.

Objective 1: To compare different treatment strategies for their perioperative mortality and morbidity, corrected for confounding physiological and anatomical characteristics, in order to account for baseline risk and indication biases.

Objective 2: To identify whether particular physiological and/ or anatomical baseline characteristics are associated with better clinical outcomes or better health economic efficiency using one or other treatment strategy.

Objective 3: To compare different treatment strategies in terms of overall survival and in terms of treatment failure in the long-term follow-up (stent-graft related complications, secondary interventions, aneurysm-related mortality).

Objective 4: To perform cost effectiveness analyses from a broad societal perspective (NHS as well as non-NHS costs) to establish incremental cost effectiveness ratios, comparing different treatment strategies in terms of life years and quality adjusted life years gained.

Objective 5: To establish the clinical and cost utility of FEVAR and of off-label standard EVAR, in patients who are considered physiologically unfit for OSR, and to compare these against medical management.

Pilot Study

We have completed a multicentre pilot study and a manuscript is being prepared for peer-reviewed publication. A short report is attached. The pilot study was valuable for three important reasons:

A) It showed that that OSR and FEVAR are not the only surgical strategies used to treat juxtarenal aneurysms; off-label standard EVAR is being used in a substantial proportion of patients. Techniques such as Chimney EVAR are rarely used.
B) It gave us experience in obtaining data regulation approvals under section 251 and managing data in compliance of approval conditions. These factors influenced our development of this proposal.
C) It enhanced our experience of running Corelab analysis of CT scans through remote access (see below).

'Corelab' (core laboratory):

Corelab refers to a combination of infrastructure and methodology of warehousing radiological imaging and methodical interpretation according to predetermined reporting standards. Clinical radiological reporting is inherently subjective and prone to inconsistencies. Uniform reporting by a 'core' group of researchers who consistently follow a predetermined set of image analysis steps and definitions is an established technique used in peripheral arterial as well as aortic aneurysm research. The pilot study Corelab consisted of CT workstations with three dimensional image analysis capabilities, connected to archive of pseudonymised study images retrieved via NHS PACS IEP. We established smooth running of this system (including retrieval from remote hospitals), archiving data in compliance with data regulation and application of imaging analysis to uniform reporting standards. Our plan is to use the same format for the proposed study.

Research Plan

Methods:

The Chief Investigator organised and led a workshop at the Vascular Society of Great Britain and Ireland Annual General Meeting 2014 with the aims of 1) reviewing methodological aspects of a study to establish the role of FEVAR, and 2) assess vascular surgeons' attitudes towards participating in a RCT. There was an overwhelming reluctance to support an RCT for the following reasons:

A) There was and still is a consensus that endovascular techniques significantly reduce the risk of perioperative death compared to OSR, at all levels of operative fitness. Furthermore, patients unfit for OSR are routinely offered endovascular techniques, for fear of aneurysm rupture. Therefore, physicians are reluctant to randomise between OSR and FEVAR or FEVAR and 'Best Medical Therapy'. Generally accepted uncertainty regarding overall survival benefit or cost effectiveness is not enough to change attitudes towards an RCT.

B) Both OSR and FEVAR operations come in a range of technical complexities. Vascular anatomies suitable for similar FEVAR configurations (with similar technical complexity of implantation) may require open surgical strategies of varying complexity, with cross clamp level ranging from infrarenal to supracoeliac, and therefore different operative risks. Similarly, juxtarenal AAAs that can be treated by OSR with the same level of aortic cross clamp may require FEVARs of varying complexity. Such heterogeneity calls for specific randomisation protocols to ensure that any one arm of a trial is not dominated by the most complex or the simplest technique of that particular type of intervention. This creates implications for recruitment and numbers as well as statistical analyses.

The NIHR HTA has independently reached the same conclusion and proposed a cohort comparison (observational) study, which was specified in the commissioning brief.

We recognise that this study design is potentially vulnerable to confounding by A) risk bias and B) indication bias (treatment allocation bias). These must therefore be accounted for, as suggested in the commissioning brief. Therefore we plan to employ appropriate statistical analysis methods to minimise confounding, incorporating:

A) quantification of individual patient operative risk using British Aneurysm Repair Score (BAR score), a validated method developed specifically for AAA patients treated in the NHS [8]. The paramaters recorded in the BAR score are:

- Age
- Gender
- Type of repaire (OSR, EVAR)
- Cardiac disease
- Serum creatinine (mmol/L)
- Sodium (mmol/L)
- ECG (normal, abnormal)
- Previous aortic surgery
- White cell count
- AAA diameter
- ASA grade

B) Detailed image analysis of anatomy to classify each patient's AAA for complexity, for both open and endovascular types of repair, through a central core laboratory. The core laboratory will review all CT scans for patients treated in England treated for an AAA and stratify patients based on the following criteria:

1) Length of neck
- 0-2 mm
- 3-4 mm
- 5-6 mm
- 7-8 mm
- 9-10 mm
- 11-12 mm
- 13-14 mm

2) Neck angulation
- 0-60
- 60-90
- More than 90

3) Neck quality
- Good
- Moderate
- Poor

After review of the above anatomical criteria and consideration of other characteristics such as inter-vessel separation the patients will then be stratified as being suitable for:

- Open Surgical Repair
    - Infarenal clamp
    - Suprerenal clamp
    - Clamp between SMA and CA
    - Supra-celiac clamp

- FEVAR
    - Seal zone above renals
    - Seal zone above SMA
    - Seal zone above CA

In order to expedite recruitment, reduce inclusion bias and improve external validity, we plan to include all patients treated in England for juxtarenal AAA through the use of routinely collected data. This will be supplemented with additional directly collected data, giving a comprehensive linked data set.

Target Population:

The term 'Juxtarenal Aneurysm' denotes an aortic aneurysm that is close to the renal arteries. Although the term was in use long before EVAR was invented, there is no universally accepted definition, even in the Reporting Standards for EVAR Research that were published in 2002 and revised in 2013 [9,10]. For this reason, the FEVAR Consensus Working Group of the British Society of Endovascular Therapy used five descriptive categories of aneurysm neck, only one of which was primarily determined by neck length. A definition based simply on the length of aneurysm neck (e.g. less than 10 mm) has the advantage of simplicity, but misses a substantial proportion of patients relevant to the problem addressed by this research as described in the commissioning brief - namely, increasing demand for fenestrated EVAR procedures and a need to establish comparative clinical and cost effectiveness against alternatives to FEVAR.

We therefore plan to use anatomical criteria that will take account of the various aspects of aneurysm neck anatomy for which FEVAR was introduced, including length, shape and quality. This study will include all potential candidates for FEVAR whose AAAs may be described as juxtarenal, pararenal and suprarenal aneurysms. The function of target vessel stents which are used in conjunction with FEVAR devices is to fix alignment of the fenestrations with the target vessel ostia and to bridge little gap between the fabric of the stent-graft body and the target vessel. When the target vessel stents are expected to bridge variable stretches of gaps between the stent-graft body and target vessels, a Branched EVAR (which is distinct from FEVAR) is normally used. Such instances are excluded from this study as those patients would be included in ETTAA study, HTA 11/147/03. The proposed study will exclude anatomical configurations that could be treated by on-label standard EVAR using any CE marked EVAR stent-graft.

Anatomical inclusion and exclusion criteria and classification for propensity scoring analyses are described in detail in the enclosed 'Anatomical and Physiological stratification'.

Health Technologies being assessed:

The current proposal will include the following treatment strategies available to manage patients with juxtarenal AAAs:

1) Open surgical repair (OSR): Conventional surgical repair using sutured anastomoses of a surgical conduit to arterial anatomy by any access approach, e.g. transperitoneal, retroperitoneal or laparoscopic.

2) Fenestrated EVAR: Fenestrated EVAR using one of the three commercial devices currently available in the UK (1) Zenith Fenestrated, Cook Medical Ltd. Hitchin, UK, 2) Fenestrated Anaconda, Vascutek Ltd. Glasgow, UK. 3) Jotec Extra-design Service, Jotec UK, Evesham, UK). Potential new introductions with CE marking / Certificate of conformity will be included subject to approval by study management.

3) Off-label standard EVAR: Treatment of juxtarenal AAA using a standard EVAR, designed for treating infrarenal AAAs outside manufacturer's Indications for Use (IFU) in relation to aneurysm neck anatomy is termed off-label EVAR in this study. Classifying aneurysm anatomy as 'off-label' or 'on-label' for a set of devices is a standard Corelab methodology and has been used in numerous studies, including the pilot study completed by our group. We plan to use a methodology referred to as 'liberal application of IFU' [11].

The three technologies named above will be included in three distinct cohorts of interventional treatment. Techniques such as Chimney-EVAR are used in such small numbers that comparison will be unfeasible and will be excluded from this study.

Medical management: Since the size criterion for threshold to offer elective repair of AAA is widely accepted as 55 mm, we do not plan to include patients with smaller aneurysms in this study. Patients with aneurysms 55mm or larger in size and who are medically managed fall into two categories:

***4)'Operation-deferred'*:** When the risk of rupture at the existing size of aneurysm (though larger than 55 mm) is considered to be smaller than the risk of death from an elective repair, a physician and their patient may wish to delay surgery until there is a change in the risk balance between aneurysm rupture and procedure related death. Such patients are observed with a view to proceeding with surgical intervention if the perceived risk of rupture increases through aneurysm enlargement. If a decision for an operation is made later, endovascular techniques are usually favoured, though not exclusively, since the patients are usually of high surgical risk. This group of patients will be included in the study.

***'Operation-declined'*:** In some patients a clear decision has been made between physician and the patient (and often their family) that an elective aneurysm repair will not be appropriate, usually due to limited life expectancy (e.g. advanced malignancy) or severe comorbidity rendering them physiologically unfit to withstand any type of operation (e.g. severe cardiac/respiratory/renal disease or combination). Inclusion of this group of patients would create a bias in favour of intervention because QoL and survival will be poor in this group due to non-aneurysm related causes. Therefore this group of patients will not be included in this study.

Note on nomenclature: The on-going ETTAA study also includes patients under medical management. Because the stated aims of ETTAA include exploration of natural history of thoracic and thoracoabdominal aneurysms, the study includes: 1) patients in whom an operation is not yet indicated on aneurysm size criteria, 2) patients in whom an operation is indicated on size, but deferred due to relative risk of operation, and 3) patients in whom an operation is declined, usually due to prohibitive risk of operation or severe comorbidity. The first two types of patients are included under one cohort in ETTAA, termed 'Watchful waiting' and the last group is called 'Conservative management'. There was confusion initially but we have clarified the nomenclature, which we believe is now settled.

Commissioning brief for this study and our proposal do not include a natural history component and so we do not plan to include patients with aneurysms too small to recommend treatment. We have explained earlier why it would be inappropriate to include patients in whom a final decision has been taken not to undertake an operation. We preferred to attribute a clear and distinctive nomenclature to UK-COMPASS patients to avoid confusion both during recruitment (many ETTAA centres are expected to recruit patients to medical management cohort of this study) and later during dissemination of results.

Design and Theoretical/Conceptual Framework

This is a collaborative research between a multidisciplinary clinical research team, the NVR and Public Health England. We have thoroughly considered the scientific as well as practical issues pertinent to delivering the research objectives as robustly as possible, as efficiently as possible.

Conceptual framework:

An empirical cohort study of comparative clinical and cost effectiveness of different strategies used in the NHS to manage juxtarenal AAAs, using routinely collected data from National Vascular Registry, Hospital Episode Statistics and the NHS Picture Archiving and Communication System Internet Exchange Portal (PACS Portal), supplemented by directly collected data.

Study design:

An observational cohort study to compare different strategies for treatment of juxtarenal AAAs, namely, open surgical repair, fenestrated EVAR, off-label standard EVAR and Medical Management 'Operation-deferred', incorporating statistical methods of correcting for confounding by physiological risk and anatomical complexity.

Clinical Service Context:

According to Hospital Quality Improvement Program (HQIP) 2015 report, AAA operations are provided in 82 NHS Trusts [1]. Ten of these centres undertake more than 10 FEVAR procedures each per year and several other hospitals provide a smaller number of FEVARs. The rest of the centres carry out OSR or off-label standard EVAR in the majority of their juxtarenal AAA patients but may refer unfit or high risk patients with highly complex anatomy for FEVAR. Based on the pilot study completed by the Principal Applicant and anatomical suitability figures in the literature, an estimated 1500-2000 AAA treated in the NHS each year should fall within the indications for a FEVAR. From available device sales figures and registry data we estimate that approximately 400 of these are treated by FEVAR using commercially available devices. The majority of people with juxtarenal AAA are in fact treated using alternative strategies. Centres undertaking high volume of FEVAR have a low volume of OSR for juxtarenal AAA and that do not have a FEVAR programme tend to have a high volume of OSR.

The variegated distribution of juxtarenal AAA treatment described above calls for particular attention in selecting study centres for recruitment as well as statistical analyses in order to gain adequate external validity and obtain results that are applicable to the majority of patients treated in the NHS. A study based predominantly in high-volume FEVAR centres is unlikely to reflect the treatment of juxtarenal AAA across the NHS. It is also widely believed that both OSR and FEVAR are associated with exceptional outcomes in some centres, calling for identification of 'Cluster effect'.

Setting:

The proposed study includes all patients with juxtarenal AAA operated on in England and will be based on routinely collected data from the National Vascular Registry, Hospital Episode Statistics and the NHS Picture Archiving and Communication System Internet Exchange Portal (PACS Portal). The data will be linked and supplemented with data collected directly from arterial centres relating to Medical Management 'Operation-deferred' and QoL data. Inclusion of all patients treated for juxtarenal AAA in England, it is expected, will eliminate potential problems with cluster effect, inclusion bias and adequacy of external validity as described above.

Sources of routinely collected data:

National Vascular Registry (NVR):
The National Vascular Registry (NVR) is a national clinical audit commissioned by the HQIP as part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP). It is run by the Clinical Effectiveness Unit of the Royal College of Surgeons of England. The NVR 2015 report estimates that at least 84% of AAAs treated in the preceding three years have been included (case ascertainment). A 2015 HTA publication based on NVR data from 2000 to 2013 reported at least 85% data completeness. These figures are likely to improve because individual surgeon level reporting is based on analysis of NVR; the profession considers it a priority to see inclusion of 100% of aneurysms treated with complete and accurate filling of dataset.

NVR includes a wide range of data pertinent to this study encompassing demographics, comorbidity, preoperative assessment, intraoperative detail, postoperative complications, duration of hospital stay and critical care use for all types of repair.

Hospital Episode Statistics (HES):
HES is a data warehouse containing details of all admissions, outpatient appointments, investigations and A&E attendances at NHS hospitals in England. This data is collected during a patient's time at hospital and is submitted to allow hospitals to be paid for the care they deliver. HES is a records-based system and is designed to enable secondary use of this administrative data for non-clinical purposes, medical research being an explicitly stated one. HES data can be linked with ONS data (for survival).

NHS PACS IEP:
Picture Archiving and Communications Systems (PACS) are digital systems for managing radiological information which are routinely used by clinical staff to review radiological images and reports every day, in every hospital. PACS contains not only radiological images to be simply viewed as they are, but also ‘raw data’ of CT scans (called DICOM data) that are essential for 3-dimentional image analysis using dedicated workstations. Images from PACS systems of NHS hospital in England can be accessed via an Internet Exchange Portal (IEP).

Data point duplication
A number of data points are repeated between NVR and HES, which will allow correction for missing patients and missing data and will improve accuracy through double checking. We will be able to prevent duplicating the same patient by using linkage data points alone or combined with operation date and centre identification. Any AAAs not entered into NVR will be captured from HES, while any patients potentially missed on HES due to coding errors will be identified in the NVR. Together, nearly 100 % of all AAA treated in England will be identified for screening for inclusion, and there is no practicable method of establishing if any AAAs treated in England will be missed by this method. This is the only method of identifying all of the juxtarenal AAAs treated in NHS.

Identification of patients for inclusion:

Patients having an elective AAA repair in England will be identified from HES Admitted Patient dataset, estimated to be approximately 4000 per year. A complete list of OPCS codes for AAA repairs will be used to filter HES data because there is no specific code available for juxtarenal AAA repair.

Every patient who undergoes an elective AAA repair has a CT scan for assessment as part of normal management. CT scans of all of these patients will be retrieved via the NHS PACS IEP and preoperative scan of each patient will be reviewed in the study Corelab using 3-D workstation according to image analysis characteristics given in the attachment labelled 'Stratification'. This will allow accurate identification of juxtarenal AAAs for inclusion, objective classification of aneurysm neck anatomy in each patient for anatomical stratification and accurate identification of infrarenal AAAs for exclusion from the study. After Corelab analysis, an estimated 1000 juxtarenal AAA will be included in the study per year.

It is not practicable to identify Medical Management 'Operation-deferred' patients from routinely collected datasets because diagnostic codes for aortic aneurysms do not distinguish small aneurysms from those which exceed the diameter threshold required for inclusion in the study (i.e. those large enough to require a treatment decision, 55 mm). Therefore, patients under this cohort will be identified through direct data collection from arterial centres.

Inclusion criteria:

1) Patients undergoing elective Juxtarenal AAA repair in England; juxtarenal AAA defined and stratified into 4 strata of anatomical complexity as specified in 'Anatomical and Physiological Stratification'.
2) Patients with a Juxtarenal AAA 55 mm or larger in size and placed on Medical Management 'Operation-deferred'.

Exclusion criteria:

1) Surgeon-modified stent-grafts and devices.
2) Emergency operations (elective operations are distinguished from non-elective ones on NVR),
3) Thoracic or thoracoabdominal aneurysms (this is a different extent/location of aneurysm disease, requiring different health technology. These treatments are currently being investigated by ETTAA study-HTA 11/147/03. Patients will be included in ETTAA),
4) Aneurysm neck anatomy suitable for standard infrarenal EVAR within IFU of any CE marked device.
5) 'Operation Declined Medical Management' patients, due to co-morbidity or patient choice.

Study period:

There will be a prospective two-year recruitment period starting on 1st Nov 2017. Follow-up data will be collected for five years after that with an aspiration for more prolonged follow-up. Recruitment and follow-up of Medical Management 'Operation-deferred' patients will continue throughout the duration of the study.

Follow-up:

Long-term follow-up data is crucially important to achieving the objectives of this study fully. A detailed section regarding the importance of long-term follow-up is included in later pages. The commissioning brief specifies a follow-up of five years, which we will deliver for patients undergoing

an operation; it will be shorter for Medical Management 'Operation-deferred' cohort due to longer recruitment. We recognise that stent-graft surveillance varies according to local practice and patients having open repair are not normally followed up in the long term. It will be possible, however, to identify late complications, treatment of complications and re-interventions from HES data.

Outcome measures:

Primary endpoints:

Early: Death within 30 days of operation or in-hospital mortality during the same admission for the operation.

Late follow-up (after 30 days or discharge whichever is later): all-cause mortality, aneurysm-related mortality.

Secondary endpoints:

Early: Paraplegia, secondary intervention (Specified), secondary intervention (non-specified, including return to operating theatre non-specified), organ system complications (specified – Cardiac, Respiratory, Haemorrhage, Limb ischaemia, renal failure requiring dialysis), other morbidity (non-specified e.g. wound dehiscence, surgical site infection), stent-graft complications (including target vessel loss, endoleak types 1, 2, 3, endoleak of undetermined type, device kinking, limb occlusion).

Late follow-up (after 30 days or discharge whichever is later): Secondary intervention, device-related renal failure requiring dialysis, target vessel loss, endoleak types 1, 2, 3, endoleak of undetermined type, endotension, device kinking, limb occlusion, device structural disintegration, distal embolisation, graft infection, graft rupture incisional hernia – untreated / operated, anastomotic aneurysm, anastomotic-enteric fistula, renal infarction. Potential effects of smoking, alcohol and depression on outcome measures.

Patient reported outcome measures (PROMs):

We plan to obtain PROMs in a representative sample of patients in the interventional treatment cohorts, commencing with approximately 40% of the patients, expecting 50% loss to follow-up, giving 5-year data on 20% of the study population. We plan to collect QoL information from all patients recruited to the Medical Management 'Operation-deferred' cohort.

Treatment satisfaction questionnaire: Based on our discussions with our PPI group, a measure of patient satisfaction with treatment they received is valuable. Therefore, we plan to include the validated aneurysm-specific treatment satisfaction questionnaire.

Resource use diary: Similar to the ETTAA Study, we plan to undertake health economic evaluation from a broad societal perspective, encompassing the use of NHS as well as non-NHS resources used. We plan to collect information regarding the use of resources and health-related events in the same lines as the ETTAA study.

Quality of Life measures: We plan to utilise generic as well as an aneurysm specific QoL questionnaire to evaluate the impact of the aneurysm and its management on quality of life. EuroQuol EQ-5D 5SL forms the main instrument. The aneurysm specific form utilised will be the Aneurysm-Dependent Quality of Life Questionnaire (Aneurysm-DQoL).

The population in this study are elderly and often frail. We have gained experience with the ETTAA study in achieving very high levels of completion of the forms by understanding with empathy and

noting at the outset if individual consenting patients would like to take assistance from one of their relatives or from research staff over the telephone in completing the questionnaires. Our research staff are always cognisant of barriers faced by some aneurysm patients in completing questionnaires and diaries. We are awaiting feedback from our PPI group regarding acceptability of frequency of QoL questionnaire administration.

We recognise that for some elderly and frail patients will not be able to return their PROMS questionnaires and we therefore plan to gather responses by face to face interviews on any appropriate occasion when such patients need to attend hospital, for their normal clinical management. We acknowledge that some patients will become too frail and elderly such that it will not be feasible to collect data by any means.

The following is a provisional schedule for operated patients:

	Pre-op/entry	1 m	3 m	6 m	1 year	Annually
Generic, EuroQuol EQ-5D 5SL	✓	✓		✓	✓	✓
AAA specific, A-DQoL	✓		✓		✓	
Resource use / health diary					✓	✓

For patients in Medical Management 'Operation-deferred' cohort, the schedule will be as follows:

	Pre-op/entry	1 m	3 m	6 m	1 year	Annually
Generic, EuroQuol EQ-5D 5SL	✓			✓	✓	✓
AAA specific, A-DQoL	✓				✓	✓
Resource use / health diary					✓	✓

Sampling:

Interventional treatment cohorts: This will be a population-based analysis; all patients undergoing repair of juxtarenal AAA in England during the recruitment period will be included, without a need for sampling.

Medical Management 'Operation-deferred' cohort: We shall approach patients for recruitment through first 4 years of the study from approximately 30 participating hospitals selected to provide adequate external validity. This cohort is anticipated to be approximately 300 in number. We will attempt to interview patients refusing to consent for recruitment with the purpose of determining if they differ systematically compared to consenting patients.

PROMS: The same hospitals will also be participating in recruiting patients undergoing surgery to contribute patient reported outcome measures. Approximately 800 patients will be consented for this, anticipating 5-year data on at least 400. Once again, we appreciate the importance of checking for potential for recruitment bias in terms of participating centres as well as patients in each centre.

Long-term follow-up

It is generally accepted that FEVAR and other EVAR techniques are associated with lower perioperative mortality compared to OSR, when corrected for physiological fitness of patients, despite notable reports in literature that claim equivalent results. The BSET consensus exercise, the methodology workshop conducted by the Principal Applicant in preparation for this study, and the ETTAA study's Delphi consensus (led by the Principal Applicant and a number of co-applicants are represented in the consensus group), all point to a unanimous agreement among surgeons, radiologists and anaesthetists that endovascular techniques are safer than OSR in the postoperative period. Important questions to be addressed in the area of juxtarenal AAA treatment by different technologies are related to long-term follow-up.

There is general acceptance that with FEVAR/EVAR, incremental gain in long-term survival will be modest compared to OSR. This is based on every RCT of OSR versus EVAR for infrarenal aneurysms reporting that overall survival became equivalent between the two cohorts in late follow-up. In the UK-EVAR Trial 1 for infrarenal aneurysms (HTA 95/02/02), the difference noted in postoperative mortality was 3% [11]. While this advantage from AAA-specific mortality was preserved, there was no difference in all-cause mortality at 4 years. Extended follow-up results (HTA: 11/36/46) available within the last few days suggest that AAA-specific mortality is estimated to be significantly worse in EVAR cohort compared to OSR at 15 years, based on extrapolation of observed rates of late failure of EVAR [13].

Because FEVAR is also prone to late failure, the implications to the current study proposal are as follows:

1) Inclusion of comprehensive and carefully selected outcome measures of interest in the follow-up to identify failure of treatment, as well as risk factors for late failure of treatment.
2) Inclusion of a robust method of identifying and comparing all-cause mortality.
3) Modification of duration and methods of follow-up.

The trends and comparison between overall survival curves of different cohorts will depend upon the magnitude of difference in postoperative mortality and incidence of aneurysm specific mortality (death from failure of juxtarenal aneurysm treatment). A follow-up of five years included in this proposal is expected to give adequate information to determine if it would be appropriate to continue further follow-up and its duration. An additional factor that determines overall survival - competing risks of mortality, is anticipated to affect each cohort equally, due to measures of correcting for biases in baseline conditions.

The value of HES data:

OSR patients are normally discharged after early postoperative clinic visit. A major advantage of utilising routinely collected data from HES in our study design is an ability to collect long-term follow-up data without the patients having to return back to a clinic for the purposes of research. As a local PI of UK EVAR Trials late follow-up, the Principal Applicant has noted difficulties in compiling long-term follow-up data accurately. Attending follow-up when it is not a normal part of clinical management is difficult for the patients, who are often elderly and frail. Further difficulties arise from having to gain access to case notes when patients receive health care and interventions in multiple hospitals due to 'choose and book' system of appointments. HES data has the dual advantage of being centralised and all-encompassing. It is arguable that it is difficult to gain accurate and complete follow-up information of several years without recourse to HES data.

Outcome measures noted in the follow-up have been listed earlier. All of these are well recorded in HES and PACS data. A comprehensive and tested list of codes and key words required to retrieve this data is attached ('Codes'). Data completeness is expected to be at least the same or better than that derived through traditional site-reported data collection. Unsatisfactory or inadequate follow-up will have implications for standard clinical care of patients in the FEVAR and Off-label Standard EVAR cohorts, and as such will be acted upon by the study DEMEC.

Statistical Considerations

Full details of the statistical approaches to be taken are included in a separate statistical analysis plan which is included as an appendix to this application. Details are provided below regarding the collection of data, an assessment of the information obtained and an analytical approach to achieve each of the stated objectives.

Sample size/Power:

Because this is an observational cohort study, power calculations are difficult to obtain since precise allocation between different treatment strategies is not known. Power calculations are therefore based on conservative estimates of likely case numbers, derived from available information.

NVR reports (2013 to 2015) confirm that approximately 4000 AAAs are operated in England each year. Based on literature describing aneurysm neck configurations for FEVAR technology and on our pilot study, an estimated 1000 to 1500 of these would be classified as juxtarenal AAAs of varying complexity in our study corelab. Interim analysis will be done after 1 year to check these assumptions. We shall seek to extend the inclusion period beyond two years if required or shortened if appropriate. It should be emphasized that we do not anticipate that an extension will be necessary.

Outline power calculations for each research objective are as follows:

Objective 1 (perioperative mortality): The primary outcome is perioperative death with the primary efficacy parameter being the odds ratio comparing FEVAR to each open repair and off label EVAR. A conservative estimate of 8% peri-operative death may be expected under an open repair (based on NVR 2015 report and GLOBALSTAR registry) with a reduction to 4 % considered clinically relevant (equivalent to an odds ratio of 0.48). This effect is slightly larger than that noted in UK-EVAR Trials. As there are two comparisons of interest (FEVAR vs. OSR and Off-label EVAR Vs. OSR), a Bonferroni adjusted two-sided alpha level of 0.025 is used. Based on these assumptions, collecting data on 2000 patients will ensure a power in excess of 80% if the allocation between treatments is relatively equal and should be preserved above 70% even if one treatment strategy is used twice as much as the other two.

Objective 2 (stratified comparative analysis of perioperative death): Based on the best available estimates, it is anticipated that 120 events (perioperative deaths) will be available from the 2000 patients included in the study. The aim is to identify anatomical / physiological characteristics for which there is a differential effect of patient outcome depending on the treatment strategy employed. We plan to use multivariable models which include propensity scores as

continuous covariates, adjusted for appropriate confounding variables and including interaction effects with treatment effect. Using the statistical rule of thumb of 10 events per variable, approximately 12 variables can be included in any single model. If, for example, a two level factor is to be investigated, main effects and interaction effects and a covariate of propensity scores will account for 6 variables, allowing for a further inclusion of other confounding variables as required.

Objective 3 (long-term survival; all-cause mortality): Estimated survival rates at 1, 2 and 4 years are 90%, 80% and 70% respectively. All patients will have a median of 5 years follow-up after entering the study. It is approximated that 2000 patients should then contribute approximately 550 events (all-cause mortality after30 days/discharge). As the study is not designed to identify a difference in long-term overall survival, again no Power calculation is provided to detect some minimum clinically relevant difference. Instead, assuming the difference between two treatment arms to be measured using a log hazard ratio it is estimated that from 550 events, a standard error of approximately 0.085 will be observed. This translates to a 95% confidence interval of length of approximately 0.34. Here a hazard ratio smaller than 0.71 or larger than 1.40 will be shown to be significant at a 5% level.

Objective 4: This is described in the health economics section.

Objective 5 (comparison of fEVAR versus medical management in high risk patients): Of the 2000 patients recruited, it is anticipated that in excess of 1000 will receive either FEVAR or off-label standard EVAR. It is not possible to estimate how many of these patients will be comparable in physiological fitness and or anatomical complexity to the cohort of Medical Management 'Operation-deferred'. It is also difficult to estimate how many patients could be recruited to the medical management group in 5 years. Our aim will be to compare overall survival between cohorts of comparable baseline characteristics using a hazard ratio. If we were to record at least 500 deaths overall, a standard error for the log hazard ratio of 0.09 will be observed.

Analysis populations: All patients undergoing elective repair of a juxtarenal aneurysm in England will be included, as well as patients whose aneurysm size has crossed the threshold for repair, but are medically managed ('Operation-deferred' group). Analyses will be carried out on all patients in the primary surgery group to which they are assigned (intention to treat), irrespective of any cross-overs (e.g. conversion to OSR due to failure of FEVAR).

Missing Data: A recently completed study using NVR data (HTA 2015; 19-32) relating to 1,124 patients reported data completeness of between 85.5% and 100% depending upon the data point, with a median completeness of 93.9%. Reports of HES data validation confirm high levels of completeness and accuracy, compared to case note review. Therefore, missing data or inaccurate data is unlikely to be a problem. A statement of principle has been proposed that covariates with small amounts of missing data (<5%) will be included on a complete case basis and covariates with a large amount of missing data (>50%) will be excluded from the analysis. Covariates with a moderate amount of missing data will be included in the analysis using multiple imputation methods (using chained equations).

Reporting conventions: Continuous data will be summarised as medians with associated inter-quartile ranges. Categorical data will be summarised as frequencies of counts with associated percentages. Analyses of the primary endpoint will be assessed using a P-value of 0.025 and associated 97.5 % confidence intervals. All other effects shall be assessed using a P-value of 0.05.

Analysis techniques*:* An overview of the analytical techniques for each objective are as follows

Objective 1 (perioperative mortality): Statistical analyses of the primary outcome will follow the principle of propensity score matching. Whilst this contrasts with the approach taken by the ETTAA study, propensity score estimation is chosen for the analysis of the primary endpoint over multi variable regression techniques as peri-operative death is rare and under such circumstances it is considered that propensity score analyses as the most appropriate means of reducing selection bias.

Propensity scores estimate the probability of a patient being given either FEVAR or OSR or Off-label EVAR strategy based on baseline clinical and demographic characteristics. Patients can then be stratified based on their propensity to receive each treatment strategy and an estimate of treatment effect then obtained which adjusts for any selection bias.

Models to estimate the propensity for each patient will be generated using multi-variable logistic modelling techniques using as candidate covariates only variables that influence simultaneously the treatment assignment and the outcome variable.

Analyses of the primary endpoint will be carried out using stratified logistic regression. Models will be stratified based on the matching of propensity scores. The key efficacy parameter of interest will be an odds ratio presented with a 97.5% confidence interval. Results will be presented as a forest plot with the odds ratio within each strata presented along with the overall effect.

Objective 2 (stratified comparative analysis of perioperative death): Multivariable logistic models will be used to investigate the interaction between the treatment effect and other physiological and/or anatomical baseline characteristics. To ensure the most efficient use of data, multivariable models will be constructed which include propensity scores as a continuous covariate and include treatment effect, physiological/anatomical characteristics and the interaction effect. Assessment of the interaction effect will be used to assess if there are differing treatment effects due to physiological/anatomical characteristics.

Objective 3 (long-term survival; all-cause mortality): To remain consistent with the analysis of overall survival in the ETTAA study, the starting point (t_0) will be measured as the time at which the treatment strategy was determined. Overall survival will be defined as the time from t_0 to death by any cause. Patients will be censored at the date of the final data lock if they have not died.

Time-to-event data will be modelled using Cox proportional hazards models. The key efficacy parameter of interest will be the hazard ratios comparing different interventional techniques. Assessment of treatment effects shall be made adjusting for key covariates of interest. Assumptions of proportional hazards will be assessed via assessment of Schoenfeld's residuals.

Objective 4: Covered in the health economics section.

Objective 5 (comparison of FEVAR versus medical management in high risk patients): Time-to-event data will be modelled using Cox proportional hazards models. The key efficacy parameter of interest

will be the hazard ratio comparing FEVAR/off-label EVAR to non-surgical management. Assessment of treatment effects shall be made after adjusting for key prognostic covariates of interest. Assumptions of proportional hazards will be assessed via assessment of Schoenfeld's residuals.

Sensitivity Analyses:

Sensitivity analyses of the primary outcome (perioperative death) will be carried out by firstly adjusting the method of estimating and including the propensity scores and secondly by analysing using a mulitvariable logistic regression techniques as opposed to propensity score methodology.

Propensity scores: Sensitivity analyses shall include propensity scores using caliper width methodology (using a caliper width of 0.02 SD) and analysing the primary outcome using conditional logistic analyses. Further analysis shall use standard logistic regression including the propensity score as a covariate in the analysis.

Multivariable logistic regression: Analyses shall be carried out which does not use propensity scores but instead adjusts for confounding effects using standard multivariable regression techniques.

Results of all sensitivity analyses shall be reported alongside the results for the primary endpoint using a forest plot.

Health Economics Evaluation

Review of literature:

The first stage of any economic evaluation is to undertake a systematic literature review to ensure that development of the economic model is effectively informed by appropriate prior literature. A detailed systematic review will identify all existing sources that may provide evidence on the comparative cost effectiveness of minimally invasive treatments. In this regard we are aware that NIHR has already funded an economic evaluation which incorporated a detailed literature review and the development of an economic model. The objective of this Technology Assessment Review (HTA - 13/09/01) was to perform a clinical and economic evaluation of FEVAR. However, the economic evaluation was not completed mainly for the following reasons:

1) The systematic review assessing the clinical effectiveness revealed no comparative analyses of satisfactory quality.
2) It was not possible to obtain other input parameters in a reliable manner within the constraints of the TAR, particularly cost of the devices used.

However, the HTA report provides invaluable guidance concerning the optimum structure and focus underlying the development of an economic model in this therapeutic area which will be used to guide our analysis.

In addition to the HTA report, our preliminary literature search identified three additional international publications undertaking cost analyses of FEVAR. None of these analyses were UK-based as they analysed costs from the perspective of Canada (2009), Republic of Ireland (2011) and France (2015). Unfortunately, none of these incorporated comparative clinical effectiveness into their analysis and hence they offer limited guidance in this respect.

Further searching identified a number of additional publications of economic analyses of infrarenal AAA treatment; (15 primary sources, three pooled analyses and one clinical modelling analysis). Each of these analyses has been reviewed to identify potential methodological issues that may arise in developing our more relevant economic model.

Population:

The population covered within the economic analysis will be the population covered by the clinical analysis. As such the study population to be incorporated into the economic model will include all patients undergoing treatment of juxtarenal AAA in England during the study recruitment period and all patients under Medical Management who have either had their surgical treatment delayed or eventually denied. The patient population will be further divided into homogenous sub-groups on the basis of clinical and demographic data to generate estimates of incremental cost effectiveness ratios (ICERs) associated with the use of FEVAR in comparison to alternative surgical strategies in comparable patient populations.

Model Development:

The economic evaluation model described in HTA TAR provides a useful template for model development in this therapeutic area. As such we will incorporate all of the appropriate elements from this source into our model. The HTA TAR also strongly supported the development of such a detailed economic model in order to generate the economic evidence that is vital to optimizing clinical and policy development in this therapeutic area. As such this research proposal provides the

opportunity, for the first time, to integrate an economic analysis within the clinical effectiveness study to assess the comparative cost effectiveness of the different treatment strategies by facilitating the incorporation of primary clinical data to inform economic model structures and parameter estimates.

The key elements of the research milestones underlying the development of the economic model include:

1) Development of an accurate and reliable model comparing costs and outcomes of fEVAR and distinct alternative strategies which captures survival and quality of life data and comparative resource use data to the National Health Service, other public sector bodies and privately borne costs.
2) All analyses will be undertaken on an incremental basis in order to generate estimates of the ICERs and compare the effect of the different structures of treatment provision on different sub-groups of patients.
3) Use of probabilistic modelling to reflect and adequately capture the effects of uncertainty in model structure and parameters in order to generate estimates of the robustness of the results obtained in the analysis.

The economic model will follow patients through each stage of their treatment pathway to uncover the comparative long-term costs and benefits (both to the patient and to the NHS) in each cohort of the study. Full use will be made of the clinical data to derive utilities for use in a long-term cost utility analysis which will generate both short and long term ICERs for each of the procedures being compared.

Perspective:

Our economic analysis will be undertaken, wherever possible, from an NHS, Personal Social Services and a broad societal perspective. In addition to direct costs and consequences to NHS, we will also endeavor to discern the extent to which a resource or care burden is privately borne or imposed on other parts of the public sector outside the NHS. A questionnaire will be used in a subgroup of patients to identify potential variations in wider resource use that may result from variations in treatment provision. A detailed analysis of this material will unlock the extent to which such non-NHS costs will vary between each of the competing treatment options.

Time horizon:

Because the impact of treatment is likely to extend throughout the remaining life of the patient, a short term as well as a lifetime model will be developed to identify, measure and evaluate the impact on comparative resource use and quality of life in early, mid and late follow-up. Such modeling will ensure that in addition to early patient response, we will also capture late complications that may vary in intensity and severity between each of the treatment modalities being evaluated. The full impact of such complications on the quantity and quality of life experienced by the patient may extend well beyond the duration of study follow up and therefore a range of techniques will be employed to extrapolate the anticipated survival and quality of life impacts over the lifetime of each patient.

Outcome measures:

A comprehensive assessment of the comparative benefits arising from each procedure will be examined utilizing a wide range of outcome measures. These measures will include perioperative

death, morbidity, intensive care usage, hospital stay, long-term survival, complications arising from each procedure and quality of Life (QoL). In order to inform the cost utility analysis and generate information on which to base the ICER analysis a sub group of patients will be requested to fill in the EuroQuol questionnaire both before and after their treatment. How this subgroup will be selected has been stated under 'Sampling'. Selection of patients, together with the comparative survival data will form the basic building blocks for our assessment of comparative outcome in terms of Quality Adjusted Life Years (QALYs). The frequency of application of EQ-5D5L and other QoL instruments will be chosen so as to balance the value of the information generated and the burden imposed on patients. Currently we are awaiting advice from our PPI representatives regarding acceptability of schedule.

Input parameters:

A range of evidence typically informs decision analytic models. Given the paucity of existing data, the data required to populate model parameters will therefore be obtained from the information generated by the proposed research project and interpreted in close collaboration with clinicians and other health professionals involved in the research. The structure of short-term model and the long-term model and the transition probabilities are illustrated. Cost data parameters specified in the HTA TAR are included in the provisional dataset.

Cost of stent-grafts, ancillary implants and consumables: There is considerable variation in the choices made by physicians, potentially resulting in wide variations in FEVAR costs. There is considerable opacity in actual prices charged for standard as well fenestrated stent-grafts, varying between hospitals due to volume discounts and variability of manufacturers' expenses in servicing each hospital. A method of 'micro-costing' in a sample of procedures in order to attributing the same costs to the rest of cohort, used in some studies from the continent is unlikely to give accurate results in the UK. We plan to retrieve implant costs from HES. Consumables costs will be compiled by ensuring that any sampling is adequately representative of variations between centres and physicians.

Sensitivity analyses:

A wide range of sensitivity analyses will be undertaken to evaluate the impact of both structural and parameter uncertainty on the results obtained in the analysis. Structural uncertainty will be assessed through altering the model structure and assumptions in a range of scenario analyses. Parameter uncertainty will be analysed through the use of both Tornado diagrams and probabilistic sensitivity analyses. In this manner the robustness of the results obtained can be ascertained in order to determine their use as the basis of future clinical and policy development in this therapeutic area.

Discounting:

In accordance with NICE guidance all future costs and outcomes will be estimated over the anticipated lifetime for each patient and will be discounted at 3.5% per year. The discount rate will be varied in the sensitivity analysis to assess the sensitivity of the results to variations in the time flows of costs and benefits.

Sub-group analysis:

Each of the patients analysed will be stratified in terms of their demographic and clinical characteristics to develop homogeneous sub-groups which will form the basis for the modelling analysis. Separate ICERs will be calculated for each sub-group of patients to enable the comparative

clinical and cost-effectiveness of the competing therapeutic interventions to be evaluated in each sub-group of patients.

Generalisability of the results obtained: External validity

To be of greatest value, any locally based research would normally have to assess its' generalisability to mainstream NHS practice through the construction of an ‘impact model’. Such a model would evaluate the extent to which the results obtained in the research can be transferred to other locations and generalised throughout the NHS. However this study undertakes a national analysis of actual clinical practice using patient level data that is already being routinely collected and hence automatically evaluates the comparative clinical and cost effectiveness of the different procedures in the context of actual clinical practice. As such the study exhibits the best possible external validity as it evaluates all patients undergoing treatment for the specified condition in the UK.

Dealing with confounding factors: Internal validity

Wherever possible the potential impact of potential confounding factors will be controlled in order to maximise, as far as possible, the internal validity of the results obtained. Strategies used in the clinical outcome analysis to improve internal validity will be replicated.

In addition a range of statistical techniques will be employed in order to ensure that a ‘like for like’ comparison is undertaken between the competing procedures generating results to guide clinical development at the national level.

Approval by ethics committees

As this is an observational study, the allocation and delivery of treatments are not altered in any way for the purpose of the study. Therefore, there are no ethical dilemmas in regard to clinical management of the patients included in the analyses.

Our pilot study provided experience upon which we have based the consent aspects of our proposal and in addition we have had the benefit of guidance from our PPI representatives.

We plan to conduct this study on the same lines as the pilot study. This involves utilising NHS number and date of birth to reterive CT scans to accurately identify complex aneurysm patients. Confidential data will be deleted once the scans have been retrieved and further management of record level information will be in pseudonymised manner. The data sources differ a little from the pilot study, but access is required to the same data points, for which the necessary ethical and data management approvals were obtained for the pilot study including section 251 approval. We will make the necessary regulatory applications through the integrated HRA approval system since the study is confined to England. The research team has extensive experience of obtaining ethical approval for numerous clinical studies and is very thorough in its approach to ethical and consent issues.

We will seek informed consent from patients contributing to Medical Management 'Operation-deferred' cohort and Patient Reported Outcome (PROMS) data. We will submit the necessary regulatory applications to the Health Research Authority (HRA). The bulk of the data required for the study, however, is routinely collected and available from HES via NHS Digital.

We have discussed with our PPI representatives any possible ethical dilemmas arising from the proposed access to NHS numbers and dates of birth of individual patients in detail. They are of the opinion that such access is acceptable on the basis of the wider quality and efficiency advantages to the study, provided there is a mechanism and reassurance in place that NHS number and date of birth will be used solely for data linkage purposes followed by pseudonymisation. The PPI representatives are strongly supportive of our proposal and their continuing input will be valuable for our submissions to the HRA for ethical and data management approvals.

Public and patient involvement

Liverpool Aneurysm Research PPI group are actively involved in on-going research supporting the ETTAA Study (HTA 11/147/03), and have agreed to support our study as well. This proposal was initially presented to the group on 2nd November 2015 with subsequent follow-up.

Our PPI representatives strongly welcomed the proposed research and assured us of their support throughout the process of grant application and if successful, with the conduct and management of the study. We have taken their advice regarding ethical issues. The PPI group have no concerns regarding treatment allocation since this is an observational study of current practice. They support the administration of QoL forms to consenting patients. They are currently considering a number of validated AAA-specific QoL forms as well as resource-use questionnaires to advise us regarding acceptability of various schedules of administration.

The PPI group considered the dilemmas arising out of access to routinely collected data for this research project, including NHS number and date of birth, without explicit and specific consent from each patient. They expressed concerns regarding cross linking of data. This was addressed to their satisfaction by a data management plan which includes pseudonymisation immediately following linkage and deletion of patient identifiable information (date of birth and NHS number). They found the use of HES pseudonym for subsequent longitudinal follow-up without the need to retain identifiable information particularly reassuring.

With appropriate safeguards in place, they felt that research using routinely collected data in the manner proposed here may have some advantages, by potentially reducing anxiety associated with being approached to participate in a prospective clinical study. They have also pointed out the benefits of data collected independent of physician or patient preference for a research study, thereby reducing bias. They welcomed the benefits of improved efficiency and improved generalisability of results across wider NHS.

The PPI have helped us review the lay summary and have also reviewed the grant application, EOI stage as well as the final proposal. Their support will be crucial not only during the study, but also after the study in disseminating the findings.

Project Management

Programme Management Group (PMG)

A PMG will be constituted to facilitate regular review of the operational aspects of the study. The group will meet approximately once a month and no fewer than 10 times a year. The meeting will take place in the Liverpool Cancer Trials Unit with teleconference facility for those unable to attend in person. The schedule will be published ahead with agenda circulated one week in advance. All of the investigators, study personnel, PPI representatives and collaborators are included.

Study Steering Committee (SSC)

The role of the SSC is to provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

Data Monitoring and Ethics Committee (DMEC)

The role of the DMEC will be to ensure appropriateness of continuing the observational study without seeking to alter clinical practice as well as overseeing compliance with data regulation and data integrity.

SSC and DMEC have been constituted by the HTA.

APPENDIX 1

UK-COMPASS DATA SETS