

# PROTOCOL

Prospective evaluation of a model to predict outcomes following  
Endovascular Aortic Aneurysm Repair (EVAR)

*Study Protocol: 565335*  
*Version 1.3, dated 27 August 2009*

## 1. CLINICAL TRIAL SUMMARY

<b>TITLE</b>	Prospective evaluation of a model to predict outcomes following Endovascular Aortic Aneurysm Repair (EVAR)
<b>INVESTIGATOR/TRIAL LOCATION</b>	Associate Professor Robert Fitridge, The Queen Elizabeth Hospital
<b>STUDY OBJECTIVE(S)</b>	<ol style="list-style-type: none"> <li>1. To prospectively evaluate and improve an interactive model for endovascular aortic aneurysm repair (EVAR) developed to allow clinicians to preoperatively predict the likelihood of individual failure based on perioperative &amp; aneurysm-related mortality, need for reintervention, type I &amp; III endoleaks and 3 year survival.</li> <li>2. To assess whether specific biomarkers are able to predict the incidence of postoperative EVAR failure and hence contribute to the predictive model.</li> </ol>
<b>STUDY DESIGN</b>	<p>Multi-centre, prospective cohort study.</p> <p>This study will aim to recruit 1000 patients from multiple sites within a 2 year period.</p> <p>Patients will attend a pre-operative appointment, followed by a postoperative review within 6 weeks of surgery, at 6 months and then follow up appointments annually. The follow up period is a minimum of 3 years, up to a maximum of 5 years.</p>
<b>STUDY POPULATION</b> <b>Main selection criteria:</b>	Patients who require elective, non-urgent EVAR repair.
<b>Total expected number of patients:</b>	1000 patients
<b>ASSESSMENT SCHEDULE</b>	<p>Vascular surgeons associated with this project will be responsible for identifying and recruiting patients at their site.</p> <p>Patients will attend a pre-operative appointment (Visit 1), at which the vascular surgeon will confirm their eligibility to participate in the study. Patients will return for their procedure (Visit 2), followed by a 6 week post-operative appointment (Visit 3), a 6 month post-operative appointment (Visit 4) and then annual reviews (Visits 5-7).</p> <p>Blood tests will be taken at visits 1, 4, 7 and if patient undergoes reintervention for their aneurysm (Refer to Table 6).</p>

<p><b>PRIMARY ENDPOINTS</b></p>	<p><b>Primary outcome endpoints</b>  Primary and secondary endpoints indicative of endograft failure are shown in Table 2. Initial and mid-term Type III endoleaks are additional primary end-points.</p> <p><b>Expected outcomes</b>  Analysis of data will be undertaken to determine whether the model of expected outcomes based on preoperative variables developed in 2007 is:</p> <ol style="list-style-type: none"> <li>1. Valid when tested against new data derived from new generation endografts</li> <li>2. Improved by the additional information collected in the course of the study</li> </ol>
<p><b>SAFETY ANALYSIS</b></p>	<p>Serious adverse events and adverse events will be recorded for each patient.</p>
<p><b>DURATION OF STUDY PERIOD:</b>  <b>Per patient</b></p> <p><b>Complete study</b></p>	<p>3-5 years</p> <p>7 years</p>

## **2. INTRODUCTION AND RATIONALE**

Abdominal aortic aneurysm (AAA) is a common and potentially fatal condition affecting approximately 5% of men and 1% of women over 60 years of age. The incidence of aneurysm disease appears to be increasing in Western countries in contrast to atherosclerotic diseases.<sup>1,2</sup> Approximately 3,000 aneurysm repairs are performed in Australia per year and as the population ages this number will increase. Approximately 1,000 deaths annually are attributed to aneurysms. Two large randomised controlled trials showed no survival benefit from early repair of AAA compared to regular surveillance in aneurysms <5.5cm in diameter.<sup>3,4</sup> Nonetheless, in the absence of an effective medical therapy, aneurysms tend to expand over time. In the UK Small Aneurysm Trial three quarters of the surveillance group (initially 4-5.5cm in diameter) had undergone AAA repair at 12 year follow-up.<sup>5</sup> Aneurysms larger than 5.5cm diameter in men and 5.0cm in women are at significant risk of rupture (10% risk of rupture per annum in aneurysms 5.5-6.5cm in diameter, 19% between 6.5 and 6.9cm and 32.5% over 7cm)<sup>6</sup> and should be repaired unless major contraindications exist.

### *Endovascular aortic aneurysm repair and complications*

EVAR has been widely practiced in Australia since the early/mid 1990s and is now considered the treatment of choice for AAA by many clinicians. EVAR has a lower perioperative mortality of approximately 2% compared to approximately 5% mortality for open repair in individuals considered fit for open surgery.<sup>7,8</sup> However EVAR has a higher mortality rate in patient groups who are not considered fit for open surgery (9% in the EVAR-2 trial which randomised patients considered unfit for open AAA repair to EVAR or no treatment, and 6.3% of ASA IV patients compared to 1.6% in ASA II patients in the ASERNIP-S study) [CIA1].<sup>9,10</sup> The durability of EVAR remains problematic, with a reintervention rate of 7 (EVAR-1) to 11 (EVAR-2) per 100 patient years to maintain aneurysm exclusion.<sup>11</sup> All large series have also demonstrated that a small percentage of patients still suffer AAA rupture despite EVAR repair.<sup>12</sup> The most common complication of EVAR is “endoleak” which is defined as the persistence of blood flow outside the lumen of the graft but within the aneurysm sac resulting in the sac being pressurised to a greater or lesser extent.<sup>13</sup> A simplified classification of endoleak is shown in Table 1. Type I and III endoleaks are associated with a high risk of aneurysm rupture and thus must be fixed expeditiously, whereas type II endoleaks (occurring following 10-20% of EVAR procedures) can be safely observed unless sac size/ volume increases. The frequency of endoleak following EVAR is such that careful imaging follow-up is required. There does not appear to be a time in the postoperative period when surveillance can be discontinued. More recently a proportion of infra- and juxta-renal AAAs with anatomical features which are not suitable for standard EVAR have been repaired with ‘fenestrated’ and iliac branch grafting.<sup>14-16</sup> The mid-term results of these procedures also requires evaluation.

### *Australian audit of EVAR*

Soon after introduction of EVAR, an MSAC report to the Australian Government failed to identify any high-level evidence pertaining to the mid or long-term outcomes of the procedure.<sup>17</sup> ASERNIP-S was commissioned to undertake an audit. Pre-operative, operative and follow-up information was obtained for 938 of the 961 (98%) patients entered on the audit database over an 18-month recruitment period between

1999 and 2001. Mortality information for patients enrolled in the audit was obtained from the Australian Institute of Health and Welfare's National Death Index (NDI) at regular intervals. All Australian deaths are registered through this system. Surgeons took responsibility for submitting data and the audit manager (CI-B) oversaw data entry, validation and checking to ensure that sound practices were used in processing personal information. Pre-and perioperative information included patient demographic data, medical comorbidities, physical characteristics of the aneurysm and associated vessels, and information pertaining to the surgical procedure. Follow-up data included patient survival, creatinine, clinical assessment, results of imaging and any relevant interventions.

#### *Development of the Predictive Model*

Table 2 demonstrates the overall outcome results from the audit. Of note is a 1.8% incidence of early death, 2.5% incidence of aneurysm-related death, 13% incidence of mid-term reintervention, 2.9% of initial and 4.5% incidence of mid-term type I endoleak and an 81% 3-year survival. A number of variables were found to be associated with these graft complications and reduced likelihood of survival [CIA1, CIA13].<sup>10,18</sup> Other groups studying large cohorts of EVAR patients have found similar associations.<sup>19-21</sup> Age, ASA grade, serum creatinine, and aneurysm size were found to be strongly associated with midterm survival (at 3 and 5 years) [CIA3].<sup>22</sup> Type I endoleaks were associated with aneurysm diameter and infrarenal neck diameter whilst the need for mid-term re-interventions was associated with gender, creatinine and aortic neck angulation (>45 degrees).

Having found a number of preoperative variables that were significantly associated with adverse clinical outcomes, we developed an interactive predictive model which allows clinicians and their patients to generate a realistic set of highly relevant outcome endpoints expected after performing EVAR for a specific individual.

The *key predictor variables* used to assess relationships with each of the outcome success measures were: preoperative aneurysm size, age, ASA rating, gender, creatinine, aortic neck angle, and infrarenal neck diameter and length. The primary endpoints used as measures of success were early death, aneurysm-related death (includes early death, death due to rupture and death within 1 month of a secondary procedure), need for reintervention (initial and midterm), type I endoleaks and 3 and 5 year survival.

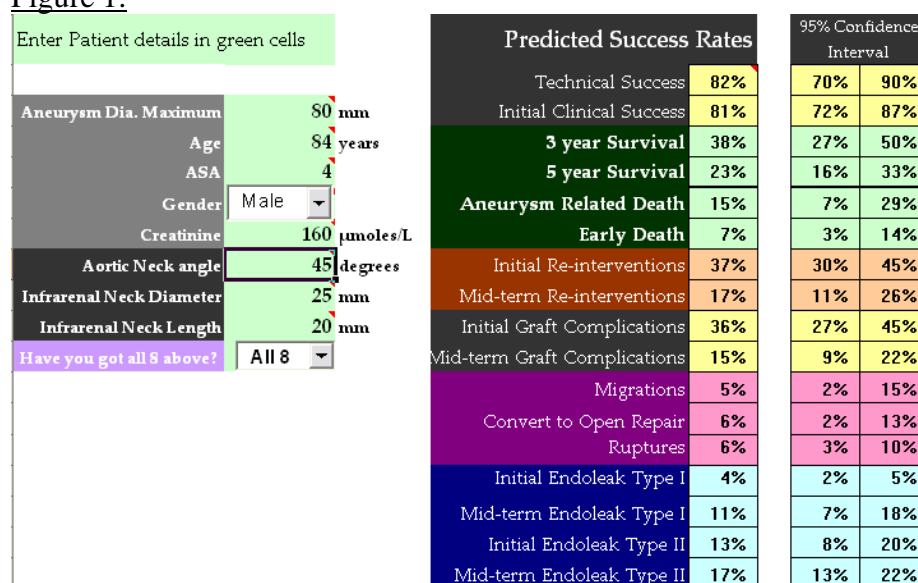
#### *Statistical analysis and modelling*

All outcome measures were binomial variables, therefore binomial generalised linear regression with the 'logit' link (sometimes referred to as logistic regression) was used to determine which key predictor variables should be included in each model.<sup>23</sup> Stepwise forward regression using the Akaike's Information Criterion (AIC) was used to select which of the preoperative variables should be included in each of the success measure models<sup>23</sup> (specifically, the stepAIC function<sup>24</sup>). For each addition of a preoperative variable in the stepwise process a statistical improvement in the model is achieved by significantly lowering the corresponding AIC. Selected models were also retrospectively examined using likelihood ratio (Chi-squared) tests.<sup>25,26</sup> However, the criteria for inclusion into models was the AIC. Table 3 lists all p-values for models of each outcome. Shading denotes which terms did not statistically significantly contribute to the model using AIC. Shaded cells list Wald p-values. Non-shaded, cells

show sequentially added, likelihood ratio p-values<sup>25,26</sup>. The largest non-shaded p-value in each row was the last term included in that particular outcome model. The le Cessie-van-Howelingen-Copas-Hosmer unweighted sum of squares test statistic<sup>25,27</sup> was applied to each of the 17 outcome models to assess the goodness of fit of each logistic model and is listed in Table 4. All primary success measures had ‘good’ fit as indicated by large p-values (p>0.05). For each of the final logistic regression models, bootstrapping was used to assess the internal model validity<sup>28</sup> (Table 4). Mortality and survival models had good predictive discrimination as indicated by high bias-corrected Somers' Dxy rank correlations. The small corrected R-squared indices indicate that models only explain a small portion of the variation. Satisfactory maximum calibration errors were observed for early deaths and mid-term endoleaks as indicated by Emax <0.01.

**The interactive model has been made available for download or online use ([www.surgeons.org/asernip-s/audit.htm](http://www.surgeons.org/asernip-s/audit.htm)).** The confidence intervals show the range within which the ‘true’ success rate for patients with the 8 attributes are expected to lie. Figure 1 gives an example taken from the interactive model of an elderly male with significant co-morbidities (including renal impairment) and a large aneurysm. His predicted five year survival is low (between 16 and 33%) and he has a 7% chance of early death following the procedure (which is nearly four times the expected 30 day mortality of 1.8% for all enrolled audit patients).

Figure 1.



### Other predictive models

A number of models have been developed to predict outcome after elective **open** AAA repair. Prytherch et al demonstrated that a simple preoperative data set (urea, sodium, potassium, haemoglobin, white cell count, age and mode of admission) is able to predict perioperative mortality and morbidity following elective open repair.<sup>29</sup> Similarly, Tang et al confirmed that this Vascular Biochemistry and Haematology Outcome Model (VBHOM) and the Glasgow Aneurysm Score (GAS) showed some predictive power for mortality but that these models did not perform as well as a more complex model which took into account **perioperative** data (Estimation of Physiological Ability and Surgical Stress (E\_PASS)).<sup>30</sup> Many ‘predictive’ models (POSSUM-based and APACHE-based) require perioperative or early postoperative data to predict perioperative mortality following open repair of AAA<sup>31</sup> and thus

cannot be used for preoperative decision making. The EVAR trial participants recently demonstrated that the Customised Probability Index (CPI), which includes the presence of cardiovascular, respiratory and renal disease and is modified by the use of  $\beta$ -blockers and statins, is able to place patients in good, moderate and poor fitness bands<sup>32</sup>. The CPI score was found to be non-linear but did demonstrate a threshold value above which mortality risk increased dramatically. GAS was also used to assess 30-day and 2-year mortality in EVAR-1 and -2 patients. GAS was found to be most useful in identifying low risk patients but of less use as a predictive tool for high risk patients.<sup>33</sup>

Many surgeons currently perform endovascular repair in sicker patients and in those with aneurysm anatomy which could be considered marginal for EVAR (or outside current recommended anatomical guidelines). Such patients are likely to have a relatively high perioperative event rate (mortality, graft-related and systemic complications), higher requirement for re-intervention during follow up and reduced long term survival. Thus a wide variation in outcomes following elective EVAR is likely in contemporary vascular practice. ***Currently our model is the only tool available to predict specific outcomes for patients prior to EVAR.*** In addition to predicting perioperative and midterm mortality, this model allows the clinician to assess whether the risk of developing a type I endoleak or need for reintervention is unacceptably high. For example, in anatomical situations where the risk of proximal graft complications is high, consideration should then be given to planning an open or fenestrated stent graft repair.

*Potential refinement of the predictive model:*

The relative simplicity of the initial data set devised in 1999 resulted in excellent compliance with data submission amongst vascular surgeons throughout Australia and has allowed the development of the predictive model using 8 data entry points which are always known to surgeons prior to undertaking EVAR. However, our hypothesis is that by collecting more detailed information regarding a patient's cardiac and respiratory disease, as well as more detailed information regarding aneurysm neck and iliac artery morphology, and more specific procedural detail it will be possible to further refine the model and hence provide clinicians and patients more useful outcome predictions for individual patients.

### **3. STUDY OBJECTIVE**

1. To prospectively evaluate and improve an interactive model for endovascular aortic aneurysm repair (EVAR) developed to allow clinicians to preoperatively predict the likelihood of individual failure based on perioperative & aneurysm-related mortality, need for reintervention, type I & III endoleaks and 3 year survival.
2. To assess whether specific biomarkers are able to predict the incidence of postoperative EVAR failure and hence contribute to the predictive model.

#### ***4. PATIENT POPULATION***

Patients requiring elective and non urgent EVAR will be enrolled on an intention to treat basis over a two year period by vascular surgeons. Participating surgeons will be asked to submit public and private practice cases. Participating units and surgeons will be active endovascular surgeons who have a track record of data submission to the previous national audit of EVAR.

Patients must also meet the following inclusion/exclusion criteria:

##### **4.1 Inclusion criteria:**

- Individuals  $\geq$  50 years of age
- Elective and non-urgent EVAR repair
- All proprietary brands, cases in which fenestrated or branch grafting is performed

##### **4.2 Exclusion criteria:**

- Ruptured aneurysms
- Patients who are mentally or intellectually impaired and cannot make an informed decision

#### ***5. STUDY ASSESSMENT AND PROCEDURES***

The following schedule summarises the activities to be undertaken at each visit. In addition to the mandated protocol visits, the optimal clinical care of the subjects must be provided at the discretion of the treating clinician.

Please note all CT and ultrasound scans performed during this study are part of the standard surgical follow up of these patients, they are not additional scans.

##### ***5.1 Demographic and baseline assessment***

Baseline characteristics will include a normal clinical and physical examination, medical history, surgical history and concomitant medications. All data will be captured in the case report form (CRF) and study worksheets.

##### ***5.2.1 Visit 1 – Screening visit (1 to 4 weeks prior to surgery)***

Having obtained written informed consent, subjects will be required to undergo a screen to determine whether they are eligible to participate in the study according to the criteria listed above. All required information will be captured in the patient source records.

Study evaluations to include:

- Inclusion/exclusion criteria assessment
- Clinical and physical examination
- Surgical and medical history
- Concomitant medications
- Pre-operative blood tests (+/- biomarkers)

##### ***5.2.2 Visit 2 – Peri-operative***

- Documentation of peri-operative details

### **5.2.3 Visit 3 – Post-operative visit (within 6 weeks of surgery)**

- Review of concomitant medication
- Assessment of any adverse events
- CT scan or Ultrasound

### **5.2.4 Visit 4 – 6 Month Post-operative Follow Up**

- Review of concomitant medication
- Assessment of any adverse events since visit 2
- CT scan or Ultrasound
- Post-operative blood tests (+/-biomarkers)

### **5.2.5 Visit 5 – 12 Month Post-Operative Follow Up**

- Review of concomitant medication
- Assessment of any adverse events
- CT scan or Ultrasound

### **5.2.6 Visit 6 – 24 Month Post-Operative Follow Up**

- Review of concomitant medication
- Assessment of any adverse events
- CT scan or Ultrasound

### **5.2.7 Visit 7 – 36 Month Post-Operative Follow Up**

- Review of concomitant medication
- Assessment of any adverse events
- CT scan or Ultrasound
- Post-operative blood tests (+/-biomarkers)

## **6. STUDY METHODOLOGY**

### **6.1 Design**

This study aims to enrol 1000 patients requiring elective and non urgent EVAR surgery.

The study will be administered by the University of Adelaide, Department of Surgery in Adelaide, under the supervision of a project co-ordinator.

A full time data manager will be based in Adelaide who will be responsible for collecting data/samples from each participating hospital in South Australia as well as administering the national database and entering data received from each state. In QLD, NSW, VIC and WA, part time data assistants (0.2 to 0.4 FTE) will be employed to assist with data collection and the collection and storage of biomarkers. These individuals will be based in academic vascular units, each of which have a strong interest in research and will provide the necessary infrastructure and IT support.

### **6.2 Data collection**

An outline of the planned data set is shown in Table 5.

Data will be collected preoperatively and at follow-up. Follow-up will be undertaken within 6 weeks of surgery, at six months, followed by annual reviews for three years.

No specific instructions regarding the modality of follow-up imaging will be given as each unit/surgeon has specific protocols based on local imaging expertise.

Approximately 10% of cases will undergo case note review. Data will be submitted on paper forms to a central office in Adelaide where it will be entered into a secure database. All due care will be made to ensure security according to the National Privacy Principles and Privacy Act. Protection for surgeons and committees will be obtained through the national Qualified Privilege Scheme. Ethics clearance will be obtained for the project, nationally and from each participating hospital.

Professor Guy Maddern will convene a data safety and management committee based in Adelaide. This committee will review trial data sets, monitor trial progress and identify problems in the study.

### 6.3 *Statistical considerations and methodology*

**Design:** The primary end-points are those listed in Table 2 plus type III endoleaks. All eligible patients are included in the analysis. This is a multicentre, prospective cohort study, which aims to develop predictive models tailored for individuals, as opposed to comparing two treatment methods. We will recruit patients for two years and collect follow up for a minimum of three years.

**Accrual:** Four primary endpoints have low incidence (<5%). With 1000 patients, we expect 18 early deaths, 25 aneurysm-related deaths, 29 initial type I endoleaks and 45 mid-term type I endoleaks based on results from the previous Australian audit. Low incidence endpoints require large sample size to be able detect differences between cohorts for building and validating predictive models. Power analysis indicates that with 1000 patients an early mortality difference of 1.2% could be detected (2 tailed, alpha=0.05, power=0.80, one sample).

**Power Analyses:** Summaries for other detectable differences for each primary success measure are provided in the following table:

<b>Primary success measure</b>	Previous rate Null hypothesis	Minimum detectable difference	Sample size
Early death	1.8%	1.2%	1000
Aneurysm related death	2.5%	1.4%	1000
Mid-term re-interventions	13%	3.1%	951
Initial endoleak type I	2.9%	1.5%	975
Mid-term endoleak type I	4.5%	1.9%	951
3-year survival	81%	3.5%	1000

Each binomial power analysis shown above is 2 tailed, one sample, with alpha=0.05, power=0.80, and beta=0.20. Type III endoleaks rates were unknown so are not shown in the table.

**Assumptions:** Mortality loss for initial endoleaks was conservatively assumed to be 2.5%. Loss to follow-up was assumed to be 4.9%, based on loss to follow-up from last audit ((961-938)/961).

**Interim analysis:** Existing models will be evaluated using new data for available endpoints. Early deaths and initial endoleaks will be available soon after procedure. 3-year survival will not be available for three years. Simple relationships between larger set of preoperative variables and available end-points will be assessed using statistical significance of logistic regressions and graphical representations of ordered subgroups. If necessary data will be transformed for model building.

**Mortality:** Australian deaths are reported through the National Death Index. This resource will be used on an annual basis, to obtain patient mortality information. This is particularly useful for patients who become lost to follow up.

**Final analysis** Existing models will be evaluated by fitting new data and assessing summary statistics for all endpoint models. Models will be improved by the additional information collected in the course of the study where Akaike's Information Criterion (AIC) is statistically significant. These data driven models will also be compared with expert experience. In addition more sophisticated model selection methods will be used to build models to see if further improvement can be gained. Goodness of fit tests (le Cessie-van-Howelingen-Copas-Hosmer) and internal validation will be performed on improved models using 200 bootstrap samples to assess the summary statistics as listed in Table 4.

**Primary outcome endpoints** Primary and secondary endpoints indicative of endograft failure are shown in Table 2. Initial and mid-term Type III endoleaks are additional primary end-points.

#### **Expected outcomes**

Analysis of data will be undertaken to determine whether the model of expected outcomes based on preoperative variables developed in 2007 is:

1. Valid when tested against new data derived from new generation endografts
2. Improved by the additional information collected in the course of the study

**Analysis - biomarkers:** We will assess the value of pre and post-operative biomarkers in predicting graft failure. We will compare the concentration of pre-operative biomarkers between subjects with and without graft failure using univariate and multivariate techniques (taking into account other determinants of graft success, such as aortic neck length and diameter). Post-operative biomarker concentrations will be plotted for patients with and without graft failure to identify whether changes in biomarker concentrations predict graft failure. As previously described for some other biomarkers we expect to see reduction in biomarkers for patients with successfully excluded aneurysm.<sup>38,39</sup> This trend is expected to be absent in patients with graft failure. Receiver operator characteristic curves and area under the curve will be used to assess the value of biomarkers in identifying endograft failure.

#### **6.4 The role of biomarkers**

Blood samples will be collected pre-operatively, 6 and 36 month post operatively. Blood samples will also be taken if the patient undergoes reintervention for their aneurysm. A number of blood test have been identified that could prove potentially important for post operative patient outcomes.

The tests detailed will be processed by clinical pathology laboratories and are standard pre operative blood tests for any patient undergoing this procedure,

- Biochemistry (creatinine, electrolytes [Na<sup>+</sup> and K<sup>+</sup>], urea)
- Complete blood exam (total white cell count)

These tests are not standard post operatively and will be additional biomarker tests.

Additional blood tests or biomarker tests will also be processed by clinical pathology laboratories,

- Lipid studies (cholesterol, triglycerides [tag] high density lipoprotein [HDL], low density lipoprotein [LDL])
- C-reactive protein (CRP)
- Plasma fibrinogen
- Homocysteine (HCY)

Another sample blood will also be collected and serum and plasma extracted. These samples will be stored at -80°C locally and later transferred to a central laboratory for batch analysis. These more specialised biomarker tests (Developmental ELISAs (Duoset, R&D Systems) have been validated to measure OPG, OPN, MDC, IL-6, IL-10 and resistin. Intra-assay coefficient of variation is <6%) will be performed at Professor Jonathan Golledges laboratory in Townsville.

We plan to assess whether specific biomarkers collected preoperatively will further enhance our ability to predict postoperative graft failure. As part of a previous NHMRC funded project Professor Jonathan Golledge identified up-regulation of two proteins osteoprotegerin (OPG) and osteopontin (OPN) which were expressed at 3-fold greater concentrations in biopsies from patients with AAA compared to those with aortic (atherosclerotic) occlusion [CIC6, CIC27].<sup>34,35</sup> The relationship between serum concentrations of OPG and OPN with AAA growth in pilot studies involving 146 and 198 patients respectively were assessed. Both serum OPG and OPN were correlated with aortic diameter change over three years follow-up (r=0.21 and 0.24 respectively). After adjusting for initial aortic diameter, smoking history, diabetes and PAD, serum OPG and OPN were both associated with AAA growth (P=0.02 and 0.001 respectively) [CIC6, CIC27].<sup>34,35</sup>

Using a range of techniques, including cytokine arrays, Western blotting, immunohistochemistry and ELISAs, and biopsies from patients undergoing aortic surgery, other potential biomarkers have been investigated. Ten cytokines were up-regulated in the body of the AAA (site of maximum dilatation) by comparison to the aortic neck. We further examined the serum concentrations of these cytokines in two cohorts of subjects screened for AAA. Serum concentration of macrophage derived chemokine (MDC) was significantly increased in subjects with AAA in both cohorts. In another study we examined the association of obesity and related cytokines with AAA presence in over 12,000 subjects [CIC22].<sup>36</sup> Serum was analysed from 952 men of whom 318 had an AAA. A 10 ng/ml increase of serum resistin was associated with

a 1.5 fold greater odds of an AAA being detected after adjusting for all other risk factors (OR 1.53, 95% 1.32-1.76). In contrast MMP-9 concentrations were not associated with AAA presence or progression. These findings suggest the likely value of OPG, OPN, MDC and resistin as biomarkers of AAA progression. Since failure of EVAR is associated with continued expansion of the aneurysm sac, **we postulate that changes in these cytokines will be diagnostic of endograft success or failure** i.e. serum concentrations of these biomarkers will reduce in patients with successfully excluded AAAs. Professor Thompson recently demonstrated that the inflammatory cytokines Interleukin-6 (IL-6) and Interleukin-10 (IL-10) are raised in individuals with AAA and levels of IL-10 are significantly reduced postoperatively. A trend towards lower levels of IL-6 was noted. As IL-6 is known to be associated with an increased risk for cardiovascular mortality, these cytokines may also be of value by contributing to predicting outcomes post-EVAR.<sup>37</sup> We will also save serum for proteomic analysis, later dividing cohorts into complicated /uncomplicated cases.

DNA will be extracted from one of the blood samples for genotyping analysis in order to study genetic variations that may be important in aneurysmal and arterial disease. The blood sample for genotyping analysis will be collected once only, ideally pre-operatively.

## **7. OUTCOMES AND SIGNIFICANCE**

The introduction of EVAR has allowed a less invasive procedure to be used in patients with anatomically suitable aneurysms. Large trials comparing EVAR to open repair have both reported mortality rate reductions of two-thirds compared to open repair with fewer major systemic complications.<sup>3,4</sup> This has led to a wide adoption of the technique and use of the procedure to repair smaller aneurysms. Surgeons also tend to perform EVAR in patients who would previously be considered unsuitable for (open) repair in view of significant co-morbidities and in individuals whose anatomy would have been considered marginal for intervention. More complex repair techniques, such as fenestrated grafts and iliac branch grafts have allowed more difficult anatomy to be treated and the influence of these techniques on outcome will be studied. However, EVAR-2, a study comparing EVAR with conservative treatment for patients who were considered “not fit” for open AAA repair found a perioperative mortality of 9% and no overall difference in all-cause mortality between the 2 groups.

The principal problems of EVAR-2 were that a number of patients “crossed over” and underwent surgery, and the subjective nature of deciding whether a patient was “fit” for open repair. EVAR-2 highlights the importance of generating individualised specific outcome predictions for individuals that take into account comorbidities and specific anatomical features of their aneurysm. The development of an interactive model to predict the likelihood of adverse outcomes following EVAR allows clinicians (and their patients) to assess the likelihood of early and mid-term success of the procedure as well as the risk of procedure-related deaths and mid-term survival.

This model is straightforward to use, being based on 8 readily determined preoperative variables (see Fig 1), and has been internally validated.

This study proposes to prospectively evaluate the model and collect more detailed information for a number of parameters which are likely to further refine the model, but were not collected during the original audit period.

The model will allow clinicians to

1. Assess the appropriateness of the procedure for a particular patient with comorbidities and anatomical features of their AAA relative to open repair or conservative treatment i.e. the natural history of the patient's aneurysmal disease can be compared to the predicted outcomes of intervention.
2. Give patients detailed information regarding the likely incidence of adverse outcomes associated with EVAR on their aneurysm rather than results of a general nature.

Currently there are no validated blood tests to assist in monitoring outcome after EVAR. We will assess the value of a number of biomarkers linked with AAA presence and progression in predicting EVAR failure. This assessment may identify new markers to incorporate in our model which can be easily measured after surgery. By validating and further refining the model clinicians, patients and health care providers will be able to make more informed decisions regarding the risks and benefits of EVAR in individual cases.

**The methodology may also be of use in developing similar models for other major surgical procedures associated with a significant incidence of adverse outcomes.**

## **8. ADVERSE EVENTS**

Adverse events associated with the EVAR procedure will be collected as part of the peri and post operative data set. Specific complications will be recorded as per the Ad Hoc Committee for EVAR<sup>13</sup>.

## **9. DATA ANALYSIS AND STATISTICAL EVALUATION**

### **9.1 Adverse Event Data**

Treatment-emergent adverse events will be listed and summarised per treatment

### **9.2 Data Recording**

CRFs will be provided for data collected from each subject. The following instructions will be followed when completing CRFs

- All forms will be filled out with black ballpoint pen
- Correction of data will be made only by drawing a single line through the incorrect entry, writing the correct values in an adjacent space and initialling and dating the correction. Incorrect data will not be obliterated using masking fluid. If corrections are made after review and signature by the Principal Investigator, they will be made aware of the changes and this awareness documented by initialling and dating the changes.
- Standard abbreviations
  - ND Test is not done
  - NR Test not recorded
  - NRQ Test not required
  - NA Not applicable
  - UK Unknown
  - NO Sample not obtained
  - SC Sample clotted
  - SB Sample broken
  - CS Clinically significant
  - NCS Not clinically significant

### **9.3 Data Quality Control**

Data recorded on subject CRFs will be subjected to a quality control review. Data from CRFs will be single entered into data spreadsheets. Resulting data listings will be independently verified for accuracy against source data. A data trail will be maintained to ensure that any changes made to entered data can be tracked. Persons responsible for any data entry, calculations and/or transcriptions will each sign and date for the work performed.

## **10. STUDY APPROVAL AND CONDUCT**

The following conditions will be met:

### **10.1 Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) Approval**

Prior to commencement of the study, the written IEC/IRB approval of the protocol and Study Information Forms/Informed Consent Forms based on the ICH Principles of GCP will be received. This approval will be typed on the Institutional letterhead and will refer to the Study Information Forms/Informed Consent Forms and to the study by title and protocol number. A copy of the signed and dated letter of approval will be obtained prior to study commencement

Protocol modifications that may impact on subject safety or the validity of the study will be approved by the ethics committee.

### ***10.2 Ethical Considerations***

This study will be carried out in accordance with the Principles of International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) (as adopted in Australia) which build upon the ethical codes contained in the Declaration of Helsinki and the Australian National Statement on Ethical Conduct in Research Involving Humans.

### ***10.3 Written Informed Consent***

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

It is the responsibility of the Investigator to obtain a written informed consent from each individual participating in the study after adequate explanation of the aims, methods, objective and potential hazards of the study. The Investigator must also explain to the subjects that they are completely free to refuse to enter the study or withdraw from it at any time. Appropriate forms for documenting a written informed consent will be provided by the Investigator.

### ***10.4 Emergency Contact with Investigator***

Suitable arrangements will be made for subject to make contact with the Principal Investigator or a medically qualified Co-Investigator in the event of an emergency.

### ***10.5 Protocol Deviations***

Only when an emergency occurs that requires a departure from the protocol for an individual will there be such a departure. The nature and reasons for the protocol deviation will be recorded in the subject's CRF.

### ***10.6 Termination of the Study***

The Principal Investigator reserves the right to discontinue the study for safety reasons at any time in collaboration with the University of Adelaide. Reasons will be provided in the event of this happening.

## **12. STUDY ADMINISTRATION**

### ***12.1 Quality Assurance***

Regulatory agencies may also conduct a regulatory inspection of this study to ensure compliance with GCP and all other applicable regulatory requirements. Such audits/inspection can occur at any time during or after the completion of the study. If an audit or inspection occurs, the Investigator and the University of Adelaide agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

### ***12.2 Records Retention***

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents as least fifteen (15) years after the completion or discontinuation of the study.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

### ***12.3 Confidentiality***

All data and information generated by each site as part of the study (other than a subject's medical records) will be kept confidential by the Investigator and other research staff associated with the study. The Investigator or other site personnel will not use this information and data for any purpose other than conducting the study.

### ***12.4 Property Rights***

All data generated by each site as part of the study (other than a subject's medical records) are the sole property of the University of Adelaide. All rights, title and interests in any interventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the site staff during the course of or as a result of the study are the sole property of the University of Adelaide and are hereby assigned to the University of Adelaide.

### ***12.5 Publication***

Proposed publications shall not include confidential information other than study results and shall not include any personal data on any subject such as name or initials.

**Table 1:** Definitions of endoleaks (from Chaikof *et al*, J Vasc Surg 2002)

<b>Endoleak Type</b>	<b>Description</b>
I	attachment site (proximal or distal) leaks
II	branch (e.g. lumbar or inferior mesenteric artery)leaks
III	graft defect (junctional leak or modular disconnection)
IV	graft fabric porosity (<30 days after graft placement)
Endotension	pressurised sac/ sac enlargement without imaged endoleak

**Table 2:** Overall success rate (ASERNIP-S audit)

<b>Primary success measures</b>	<b>n</b>	<b>Overall</b>	<b>Secondary success measures</b>	<b>n</b>	<b>Overall</b>
Early death	17/961	1.8%	5-year survival	651/961	68%
Aneurysm related death	24/961	2.5%	Initial clinical success	854/961	89%
Mid-term re-interventions	118/938	13%	Technical success	890/961	93%
Initial endoleak type 1	28/961	2.9%	Initial re-interventions	299/961	27%
Midterm endoleak type 1	42/938	4.5%	Initial graft complications	242/961	25%
3-year survival	774/961	81%	Mid-term graft complications	102/938	11%
			Migration	21/961	2.2%
			Conversion to open repair	23/961	2.4%
			Rupture	16/961	1.7%
			Initial endoleak type 2	67/961	7%
			Midterm endoleak type 2	132/938	14%

**Table 3: Model p-values**

<b>Preoperative variables</b>	Aneurysm Diameter	Age	ASA	Gender	Creatinine	Aortic neck angle	Infrarenal neck angle	Infrarenal neck length
<b>Outcome</b>								
Early death	0.001	0.070	0.317	0.433	0.803	0.179	0.285	0.413
Aneurysm-related death	<0.001	0.284	0.030	0.844	0.698	0.924	0.490	0.374
Mid-term re-interventions	0.330	0.975	0.688	0.045	0.029	0.014	0.651	0.491
Initial endoleak type I	0.406	0.663	0.491	0.568	0.870	0.436	0.635	0.007
Mid-term endoleak type I	0.005	0.512	0.732	0.862	0.263	0.674	0.130	0.894
3-year survival	<0.001	<0.001	<0.001	0.199	0.002	0.962	0.300	0.888

Significant terms list likelihood ratio p-values. Shaded non significant terms list Wald p-values; p-values are displayed because they are more readily understood than reduction in AIC.

**Table 4: Global goodness of fit test and validation summary results of primary endpoints**

<b>Primary success measure</b>	Goodness of fit p	Validation Results		
		Corrected Dxy	Corrected R2	Corrected Emax
Early Death	0.92	0.384	0.058	0.007
Aneurysm Related Death	0.53	0.497	0.099	0.022
Mid-term Re-interventions	0.13	0.170	0.016	0.075
Initial Endoleak Type I	0.59	0.310	0.026	0.142
Mid-term Endoleak Type I	0.32	0.255	0.038	0.001
3 year Survival	0.57	0.405	0.115	0.017

**Table 5: Data collection**

<b>Planned data items for EVAR project – Initial data set (not including follow up)</b>						
Patient name	Date of birth	Gender	Height	Smoking status	ASA	
Weight	Medical record #	Surgeon name	Hospital	Biochemistry (creatinine, electrolytes, urea)	Complete blood exam (total white cell count)	
Smoking status	Exercise tolerance	ABI	Foot pulse palpable	First degree relatives with AAA		
<b>Cardiac assessment</b>						
a. asymptomatic with normal ECG		b. asymptomatic, but with either MI >6 months ago, occult MI on ECG or fixed deficit on stress test (tetrafosmin (TF)/ dobutamine stress echo (DSE))				
c. Any one of: stable angina, no angina but reversible perfusion defect on TF or DSE, significant silent ischaemia (1% of time) on Holter monitoring, Ejection fraction (EF) 25-45%, controlled ectopy or asymptomatic arrhythmia, history of congestive heart failure (CHF) which is now controlled.			d. Any one of: unstable angina, symptomatic or poorly controlled arrhythmia, poorly controlled or recurrent CHF, EF<25%, MI within 6 months.			
<b>Respiratory assessment</b>						
a. Asymptomatic, normal CXR, Pulmonary function tests (PFTs) within 20% predicted			b. Asymptomatic or mild exertional dyspnoea, mild parenchymal changes on CXR, PFTs 65-80% predicted			
c. Between b and d.		d. Vital capacity less than 1.85 litres, FEV1 < 1.2 litres or < 35% of predicted maximal voluntary ventilation <50% predicted, pCO2 > 45 mm Hg, supplemental o2 use necessary or pulmonary hypertension.				
<b>Other comorbidities</b>	Hypertension	Stroke / TIA	PVD			
Diabetes	Dialysis	Hepatic disease	Haematological disease			
<b>Medication</b>	β blocker use (and resting heart rate)	Statin use	Warfarin			
<b>Features of neck / aneurysm, etc</b>	Max diameter	Infrarenal neck length	Infrarenal neck parallel or funnelled			
Infrarenal neck diameter	Aortic neck angle	Thrombus in neck; % of cross-sectional area	Aneurysm angle			
External iliac artery diameter	Saccular aneurysm	Iliac aneurysm	Occlusive aorto-iliac disease			
Iliac tortuosity	Iliac calcification	Artery affected by aneurysm	Patency of IMA			
<b>Imaging</b>	Spiral CT	MRI	Ultrasound	Abdominal X-ray	Other	
<b>Operative</b>						
Date of admission/ procedure/ discharge			Device type	Device name		
<b>Planned additional procedures</b>						
Proximal fenestration(s) - # of vessels; name of vessels						
Internal iliac embolisation and graft to external iliac art - side						
Iliac branch graft - side		Inferior mesenteric artery embolisation	Iliofemoral graft or crossover			
<b>Unplanned additional procedures</b>						
Stent/ extension graft to proximal neck			Stent to body or distal end of graft			
Extension to external iliac +/- embolisation internal iliac art			Iliac art repair/ iliofemoral bypass/ crossover			
Conversion to open repair			Other - If yes, describe			
<b>Complications</b>						
Death	Vessel complications	Failed deployment	Misplaced deployment			
Imperfect seal	Twist/kink/obstruction	Embolisation	Failed access	Other		
<b>Post operative complications</b>						
Endoleak (I-IV)	Endotension	Migration - distance	Graft infection/thrombosis	Other		
<b>Biomarkers</b>						
Lipid studies (Chol, tag, HDL, LDL)	CRP	Plasma fibrinogen	Homocysteine	Serum	Plasma	DNA

**Table 6:** Visit Schedule \*\*\*Also take bloods if patient undergoes reintervention for their aneurysm.

	Visit 1 (pre-op visit)	Visit 2 (peri-op visit)	Visit 3 (6 week post-op)	Visit 4 6 M (post-op)	Visit 5 12 M (post-op)	Visit 6 24M (post-op)	Visit 7 36M (post-op)
Informed Consent	X						
Patient Demographics	X						
Inclusion/Exclusion Criteria	X						
Medical/Surgical History	X						
Physical Examination	X						
CT scan or Ultrasound	X		X	X	X	X	X
Adverse Event Recording			X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X
***Blood Test: Blood Biochemistry (creatinine, electrolytes [Na <sup>+</sup> , K <sup>+</sup> ], urea), Complete blood exam (total white cell count)	X			X			X
***Biomarkers (to be processed by clinical pathology laboratory): Lipid studies (Chol, tag, HDL, LDL), CRP, Plasma Fibrinogen, Homocysteine	X			X			X
***Biomarkers (to be sent to Prof. Jonathon Golledge laboratory, Townsville): Serum, Plasma, Genotyping	X			X			X
Peri-operative data collection		X					

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