# IMPROVE

## Can eEVAR reduce mortality from ruptured AAA?

# PROTOCOL

Powell & 12 co-applicants

**1 Can emergency endovascular aneurysm repair (eEVAR) improve the survival from ruptured abdominal aortic aneurysm?**

**2 How the project has changed since the outline proposal and initial full proposal**

The outline proposal was for a cluster trial at the level of the ambulance service to be followed by in hospital randomisation of patients with clinical diagnosis of ruptured abdominal aortic aneurysm (AAA) to either a strategy of endovascular aneurysm repair or to normal care with open repair. The Board requested that a full proposal focus on a Randomised Controlled Trial for open repair against endovascular repair only. We have followed this guidance. Since the outline proposal there have been 2 systematic reviews of the topic and a Cochrane review, all lamenting the lack of randomised trial data for endovascular versus open repair of ruptured AAA. The best quality review reported on the outcome of in-hospital mortality. We have consulted widely, including with patients to seek their views on trial design and relevant outcome measures: in-hospital mortality was more important to patients and their families than was 30-day mortality. However, the Emergency Care Board was keen for us to retain 30d mortality as the primary outcome: the Board also has recommended a 1:1 randomisation rather than the 2:1 randomisation we had considered. We also have been able to base the percentage of patients anatomically suitable for endovascular repair on the systematic review data and access unpublished data from a pilot trial in Nottingham to indicate the percentage of patients with a hospital clinical diagnosis of ruptured AAA who do not have an aneurysm. Based on these changes, we still need a large trial of about 600 patients and therefore have an extended recruitment period (by 12 months). The costs of the trial have been revised in line with these changes and other suggestions from the Board.

***3*** **Planned investigation**

***Background***

Without intervention ruptured AAA is fatal and the overall mortality exceeds 85%. About half of patients with ruptured aneurysms die in the community. Half of those patients arriving in Accident & Emergency do not reach the operating theatre alive. Among the patients who reach the operating theatre (for open surgical repair under general anaesthesia), only half will leave hospital alive. These stark figures have changed little over the last 50 years [1].

Ruptured aortic aneurysms are the 13$^{th}$ commonest cause of death in the UK, responsible for 12,000 deaths per year, with infra-renal abdominal aortic aneurysms (AAA) causing 8,000 of these deaths. The incidence of both AAA and ruptured AAA continues to increase year on year [2]. The incidence of ruptured aneurysm is increasing in women too [3]. Routine practice is to direct patients suspected of having a ruptured AAA directly to the operating theatre for open repair, without pre-operative CT scan. In England there are about 1300 open surgical repairs for ruptured aneurysm each year, with 30-day and in-hospital mortality being similar at 47-8% [1,4,5]. This mortality appears independent of hospital volume, although this may be influenced by case selection [6].

The in-hospital care of these patients is costly, as many days are spent in the intensive care unit (a mean of 3.5 days for uncomplicated cases & 9.5 days in complicated cases) and the average hospital stay is long. Recuperation after discharge following open surgery for ruptured aneurysm can take up to 6 months, with further impact on the resources of the family, social care and general practice.

The mortality for endovascular repair of ruptured AAA may be much lower and some have suggested that this should become the new gold standard treatment of ruptured aneurysms [7]. Also, the in-hospital and 1-year costs of treating ruptured aneurysms by endovascular repair may be up to 40% lower than for treatment by open repair [8].

***The principal research question to be addressed***

**Can a strategy of preferential endovascular repair of ruptured AAA, versus the current practice of open repair, significantly reduce the 30-day & in-hospital mortality of ruptured AAA?**

***A Existing research - Evidence from Cochrane and systematic reviews***

A 2007 Cochrane review [9] of emergency endovascular aneurysm repair (eEVAR) for ruptured AAA has highlighted the lack of randomized trials versus open repair: most of the reported studies have been in selected patient series, often without contemporary controls and there has been only one small pilot randomized trial [10]. The 30-day mortality rate of the studies reviewed ranged from 0-39% for eEVAR, which was associated with reduced needs for transfusion and hospital stay [9]. Another systematic review suggested that the pooled estimates of 30-day mortality from eEVAR and open repair were 22% and 38% respectively, crude odds ratio 0.45 [95%CI 0.28-0.72], but after adjustment for haemodynamic status there was no difference in mortality: the most haemodynamically stable patients were selected for eEVAR [11]. However, there are arguments that the greatest benefit for eEVAR will be in the unstable patients [7]. In the most recent and rigorous systematic review, with meta-analysis, heterogeneity and sensitivity analyses, the focus was on in-hospital mortality. The pooled estimate for in-hospital mortality was 21% [95%CI 13-29] and of the patients assessed with CT for endovascular repair 56% (49%/88%) were anatomically suitable [12]. These authors also point out that it is likely that a care algorithm specifying permissive hypotension, CT scanning before intervention, anatomic eligibility criteria similar to those for elective repair and a trained team significantly improves the results of eEVAR [12]. In one centre application of such an algorithm reduced in-hospital mortality for eEVAR from 29% to 13% [13].

***B Existing research 2009 - Why is this trial needed now?***

1) A Cochrane review and 2 systematic reviews, all in the last few months, have indicated that endovascular repair of ruptured AAA could be associated with an important early survival benefit, but these findings could be accounted for by the difference in haemodynamic status between the eEVAR and open repair patients [9,11,12]. All reviews stress the need for a randomized trial: the first two reviews indicate that eEVAR could be associated with a reduction in mortality of at least 20%. The most recent review from McMaster University, Canada, focusing on in-hospital mortality, concludes "*we believe that the evidence summarized here is inadequate to recommend widespread adoption of strategies that include REVAR (EVAR for ruptures), and that a large multicenter randomized trial comparing such a strategy with open repair is needed*" [12].

2) There is equipoise amongst vascular interventionalists about the potential benefits of eEVAR.

3) MASS and other trials have shown how screening elderly men can reduce the incidence of aneurysm rupture [14]. All vascular surgeons are delighted that aneurysm screening for all men in the UK at the age of 65 years has been announced, although it may take about 10 years to establish this programme and its full impact on AAA rupture will not be achieved for 15 or more years. Even then, aneurysm rupture will not disappear, since many men at highest risk will refuse screening and women (in whom the incidence of AAA is 3 times less than in men) will not have been screened.

4) There is an established collaborative network of experienced vascular surgeons and interventional radiologists participating in the UK EVAR trials for elective repair of large, intact AAA [15,16] which will complete in 2010. Several of the trial centres now have teams trained for eEVAR.

Therefore, the decision to seek randomised trial evidence about the use of endovascular repair in ruptured AAA is timely, there is an established research network, clinical equipoise, sufficient experience and recruitment will be optimal in the years before national screening takes effect.

***C Trials currently underway***

One small randomized trial of endovascular versus open repair for ruptured AAA is underway, the AJAX trial in Amsterdam, supported by the Dutch Heart Foundation [17] and the ECAR trial is running in France. Both trials are small and only randomize haemodynamically stable patients who are known to have an aortic anatomy suitable for endovascular repair. Neither of these trials addresses the most important issue, for both patients and the health service, of whether a strategy of preferential endovascular repair should be applied to all patients with a clinical diagnosis of ruptured aneurysm (see reference 12). AJAX randomised 116 stable patients, who already had undergone CT scan to ensure suitability for eEVAR, to either endovascular or open repair. The primary end-point of morbidity and mortality at 30 days was similar in the open and endovascular repair groups, 47% and 42% respectively [presentation at 34$^{th}$ Charing Cross Symposium]. Even in 2008, a principal investigator from this trial has called for large trials in which less haemodynamically stable patients are recruited [18]. In Paris, the ECAR trial proposes to recruit about 160 stable patients with aortic anatomy suitable for endovascular repair and is to be based on the weak methodology of randomizing the treatments available in the participating hospitals week by week, which avoids the dilemmas about obtaining informed consent from critically ill patients. The primary outcome is 30-day mortality and the trial is powered on a ≥25% mortality difference between the randomized

groups and the trial plans to report in late 2014. Searching on www.controlled-trials.com, www.clinicaltrials.gov & networking with international colleagues has revealed no other planned trials.

***The proposed trial***

Patients with a clinical diagnosis of ruptured AAA will be individually randomized, in either Accident & Emergency or the vascular reception unit, to either a strategy of preferential endovascular repair (n=300) or normal care with open repair (n=300). The strategy of endovascular repair necessitates rapid access to CT angiography to confirm rupture and determine anatomical suitability for endovascular repair. The majority (55-66%) of patients with ruptured AAA will be considered anatomically suitable for endovascular repair and then receive this treatment. Remaining patients with ruptured AAA will undergo open repair (Figure 1). All patients will be followed for a minimum of 3 years for major morbidities, health service costs and mortality. After consultation with patients and their families (who unanimously viewed coming home alive as the most important consideration), we have retained in-hospital mortality as a key outcome, but in line with recommendations from the Board have altered our primary outcome measure to 30-day mortality.

***Outcome measures***

Primary: 30-day mortality

Secondary: 24-hour, in-hospital, and 1-year mortality, time from admission to AAA repair, complications and re-interventions related to ruptured AAA repair in 1 year, other major morbidity (stroke, myocardial infarction, renal or respiratory failure) in 1 year, diagnostic accuracy, patient disposal, costs and cost-effectiveness. 3-year cost-effectiveness analysis will also be undertaken, (with a formal request for trial extension).

***Planned interventions***

Our strategy for eEVAR is the novel intervention. This involves urgent CT angiography to confirm the diagnosis and plan endovascular repair whenever feasible: endovascular supracoeliac aortic balloon occlusion will be used to support less stable patients. Guidelines for anatomical restrictions to endovascular repair are given in Appendix II. Patients will then be transferred to the intervention suite or operating theatre. For those in whom aortic anatomy precludes endovascular repair, open repair will be performed. A minority of patients (~5%) will not have an AAA identified on CT scan, although another diagnosis may be indicated: these patients will be directed to appropriate care. Most of the endovascular interventions will involve an aorto-uni-iliac graft with subsequent femoro-femoral cross-over graft, with contralateral iliac occlusion. Interventional control of the aorta can be achieved using local/regional anaesthesia, with general anaesthesia being used later in the procedure as necessary. A few patients will not require a critical care bed post-operatively. The core laboratory will assess the technical success of the procedure from the post-operative CT scan, 3 months after intervention.

The control intervention is the standard current practice of open repair, with most patients, including all the less haemodynamically stable patients, being taken directly to the operating theatre for laparotomy and open repair without confirmation of ruptured AAA by diagnostic imaging (although AAA may have been confirmed by ultrasonography). Aneurysms will be repaired by cross-clamping the proximal aorta and then inserting a prosthetic inlay graft. The very stable patients may undergo diagnostic imaging before laparotomy. At laparotomy a minority of patients will not have ruptured aneurysm, some may have AAA without rupture and some may have no aneurysm. All laparotomies will be conducted under general anaesthesia and patients will require a critical care bed post-operatively. There will be no requirement for post-operative CT scan unless this is indicated clinically.

Both experimental (endovascular) and control (open surgery) interventions will follow an integrated care pathway from ambulance through Accident & Emergency, based on the JRCALC 2006 guidelines for abdominal trauma [19], see Appendix II. These guidelines limit fluid resuscitation in conscious patients with a palpable radial pulse with permissive hypotension (70-80 mm Hg). Physiological viability will be calculated for all patients using the Hardman index [20]. Guidelines will be provided for anaesthetic and critical care (Appendix II). Post-operatively statins will be recommended for all patients.

***Frequency and duration of follow-up***

All patients with ruptured AAA will be reviewed as an outpatient at 3 months (if they have been discharged) and again at 1 year after aortic repair. EQ-5D questionnaires for quality of life will be administered at 3 months, 1 year and again mid-term (between 2.5 and 4 years) after AAA repair. Patients with endovascular repair will require one post-operative CT scan (at 3 months after repair) and then the local follow-up for patients with endografts, usually requiring either CT or duplex scan at 6 months and 1 year. During the first year information also will be collected on complications and interventions relating to ruptured aneurysm repair as well as major morbidities (e.g. myocardial infarction, stroke, renal failure & dialysis) or hospitalizations from other causes. All randomised patients, with or without rAAA will be flagged with NHS Information Centre for cause and date of death, based on the pre-operative consent (conditional NIGB approval shown in Appendix IV).

***Arrangements for randomization***

Randomisation will be available at all times (24/7) by either telephone or internet using the services of thesealedenvelope.com: randomisation will be stratified by site and gender. For every patient randomized to normal care (open repair), 1 patient will be randomized to a strategy of endovascular repair. Randomisation will use a variable block size. This is a surgical trial of conventional versus a strategy of minimally invasive surgery, so patients & carers cannot be blinded to treatment allocation.

***Inclusion and exclusion criteria***

The trial will include all non-moribund patients with a clinical diagnosis of suspected ruptured AAA in Accident & Emergency. This will include patients transferred from other hospitals with a diagnostic CT scan, with patients to be randomised before suitability for endovascular repair is assessed. There will be no formal age limits.

Patients with known connective tissue disorders (eg Marfan syndrome), with known previous elective AAA repair, rupture of an isolated iliac aneurysm and with aorto-caval or aorto-enteric fistulae will be excluded. Deeply unconscious patients, very ill patients not able to survive CT-scanning and those previously assessed for elective EVAR will be excluded.

***Proposed sample size***

We will randomise 600 patients, half to immediate open repair and half to CT scan followed by eEVAR if anatomically suitable and open repair if not anatomically suitable. **The trial, comparing the groups as randomised, would have 90% power to detect (as significant at 5%) a difference in mortality of 14%.** This is based on estimated 30-day mortalities of 47% and 21% for patients receiving open repair and endovascular repair respectively, an estimate of 55% of patients being anatomically suitable for eEVAR after CT scan and that 5% of both randomized groups will not have ruptured AAA (identified only after randomisation, 5% figure taken from unpublished data of the pilot Nottingham trial). The estimated mortality is 44.6% in the open repair group and 30.4% in the EVAR first strategy group.

The estimates for 30-day mortality after open repair and proportion suitable for eEVAR may be conservative. First, the mortality rate is likely to include a proportion of patients with a rupture contained within the aortic wall or acute unruptured aneurysm for which the mortality is much lower than for ruptured aneurysm. Second, recent reports suggest that in an emergency situation more than 70% of patients are suitable for endovascular repair, aneurysm necks as short as 5mm being treated successfully [7,21,22]: if so the trial would need many fewer patients. Extension of the Cochrane review data indicated that overall 67% [range 34-100%] of patients were suitable for endovascular repair [23]. There will be differences in practice in the different centres participating, with some finding about 54% suitable for endovascular repair (as in the EVAR trials [14,15]) and some centres finding 70-80% suitable for endovascular repair [7,21,22]. Third, adjunctive balloon-expandable stents or some newer endografts may permit increasing use of endovascular repair in angulated necks [24,25].

***Planned recruitment rate***

There are 1300 operations for ruptured AAA each year in England alone [26]. When all centres are operational we had planned to recruit up to 320 patients/year (average of 20 patients per named centre/year): a period of 27 months is allowed for recruitment. This recruitment is based on audit of the annual number of repairs conducted for ruptured AAA at the centres which already have expressed interest in participation, with an allowance for non-recruitment of ~25% of patients for operational or consent reasons, see Table 2 in Appendix I. By 2011, it was clear that nationally the incidence of aneurysm rupture was declining rapidly. Therefore in 2011 a revised recruitment target (15 patients per month) was calculated. The large ambulance trusts (e.g. London & Yorkshire) already implement a policy of taking patients with suspected rupture to a vascular centre, provided the running

time is not excessive. Through local collaborative networks this policy can be applied to direct an increased number of patients with suspected ruptured aneurysm to the trial centres. The trial manager & management committee will focus on the challenging issues of governance and recruitment for the trial.

***Patient compliance and loss to follow-up***

Patient compliance is not an issue in a trial of emergency intervention. Patients will be flagged with the Health and Social Care Information Centre (previously NHS Information Centre) to ensure that post-discharge mortality data can be obtained: this includes patients who are subsequently identified as not having a ruptured AAA. After discharge, the trial will only actively follow-up patients with a confirmed diagnosis of rAAA for hospital and health economic data. It is anticipated that a minority of these (10%) will not attend for 1 year follow up, based on observations from the EVAR trials [15,16]. The ED-5Q questionnaire can be mailed to such patients not attending for 3m or 1 year follow ups. One later EQ-5D questionnaire at between 2.5 and 4 years after randomization will support mid-term cost-effectiveness evaluation: questionnaires will be mailed to surviving patients on a quarterly basis, immediately after the regular update of death reporting for the trial from Data Linkage and Extract Service.

***Cost measurement***

Microcosting methods will be used to record the costs associated with either intervention. Detailed information will be collected on the surgery undertaken for both patient groups including the stents used, time in theatre, use of blood products, contrast agents and endografts. All post operative interventions will be recorded, together with the days in hospital (critical care, general medical wards). These resource use data will be combined with appropriate unit costs. Previously collected detailed unit costs will be available (EVAR 1 and 2 trials), which will be updated during site visits to individual trust finance departments, and supplemented by unit costs from the NHS *Payment by results* databases. The impact of the surgical method on subsequent morbidity costs will be assessed. Each day in critical care will be assigned to a health care resource group (HRG) using mandated data collected for the critical care minimum dataset (CCMDS). These activity data will be combined with unit cost per hospital bed-day (by HRG) from the NHS *Payment by results* database. Readmissions will be recorded. The use of personal health services will be recorded by adapting previously developed questionnaires [27], and administering them at one year post randomisation. Community service use will then be valued using unit costs taken from published sources [28].

***Number of centres involved – 30 includes Royal Free***

30 large centres have agreed to participate, but there are another 24 centres participating in the EVAR trials, some of whom are interested in participating e.g. Truro. All participating centres will have to satisfy key entry criteria for the trial, which will include emergency access to CT scan, willingness and ability to perform EVAR 24/7 and audited results for EVAR. All the centres listed have some experience of eEVAR for ruptured aneurysm. Early results from Cambridge and the Royal London hospital, albeit reporting a selected series of patients, indicate that their mortality for eEVAR is ≤15%.

***Trial management, coordination, data checks and audits***

The trial will be conducted according to the MRC Guidelines on Good Clinical Practice in Clinical trials, with a formal linkage to the International Circulatory Health group of Imperial College, which has provisional registration with UKCRC, to ensure staff support and training and careful monitoring of trial data. A Trial Steering Committee and a separate Data Monitoring and Ethical Committee will be established before the trial commences. The trial management committee (applicants and trial manager) will be responsible for recruitment and the proper running of the trial. Each centre will be checked for eligibility (at least 3 previous eEVAR procedures, appropriate organization) and receive a training visit. Each participating centre will nominate a local trial co-ordinator who will be responsible for reporting the data on all patients with ruptured aneurysm at that centre on a web-based case record system. The trial manager periodically will visit the trial centres to provide refresher training on taking consent, monitor patient consent and data quality.

***Pilot feasibility study***

This has been conducted in Nottingham and the results published [10]. First this trial showed clearly that a diagnostic CT scan neither resulted in increased mortality nor delayed the time to definitive procedure. Second, the Nottingham study demonstrated the feasibility of a randomised trial, with randomisation prior to CT scan, but was under-powered, underscoring the need for a multi-centre trial design. Third, an effective strategy for patient consent was developed. In that study, the authors addressed a number of the issues which will be relevant to the

current application. The trial received local ethical committee approval (with support from a local ethics forum) for witnessed verbal consent. Patients to be enrolled in the trial were read a standard consent from cards which were available in the Accident & Emergency Department. Verbal consent was witnessed by an unrelated health professional (usually a nurse) acting as patient advocate. The patient advocate signed the consent form.
Before the Nottingham trial major concerns were expressed by vascular surgeons regarding the transfer of patients with ruptured aneurysm to a CT scanner. However, unpublished data (see table 2, Appendix I) suggest that patients deemed so "unstable" that they should be transferred directly to the operating theatre for operative repair have a dismal outcome. During the trial, 4 patients had severe haemodynamic instability and were not entered in to the study but transferred directly for open surgery: none survived.

***Ethical issues to be addressed***
Underlying all research studies are three ethical requirements: respect for autonomy, beneficence and justice. Patient autonomy is maintained with the help of informed consent of the subject.
The Council of Europe Convention on Human Rights and Biomedicine states that *"When, because of an emergency situation, the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned."*
This approach to consent is frequently used in patients undergoing standard open repair of ruptured aneurysm [29]. In this trial, perhaps for the first time, we shall be able to be advised of advance patient directives, via linking home address to GP data base, so that the wishes of those who do not wish for resuscitation or life-prolonging treatment can be respected.
Informed consent in emergency ruptured AAA research is, however, likely to present a number of difficulties. First, patients are frequently in hypovolaemic shock and pain, which may be associated with a reduced level of consciousness. Second, even if they are conscious and alert they are in the midst of a medical crisis, which may affect judgment. Third, due to the urgency of their clinical condition they may not have sufficient time to consider their options (unlike elective research studies where patients are offered a 'cooling off' period to consider their options.) Similar consent issues have been confronted in other emergency research studies, notably in intensive care units (e.g. myocardial infarction or head injury), on patients undergoing resuscitation or in acute stroke [30] and in the pilot Nottingham trial of endovascular repair of ruptured aneurysm on which our ethical application will be based [10]. For talking, conscious patients A patient information sheet (see example, Appendix III) will be read to the patient, to determine first whether they wish to go ahead with a procedure to stop the aortic bleeding. If the answer from the patient is in affirmative, the patient will be read the next section of the information sheet and asked to participate in the trial (see example). This approach should provide patients with sufficient information to make an informed decision and act voluntarily. It is important that patients are able to give their consent freely and are able to withdraw from the study at any time without reason. For patients unable to give informed written consent, we shall approach a relative to give consent on behalf of the patient, if this fails we shall approach either carers (in England & N Ireland) or a Welfare Guardian (in Scotland) to give consent (previous example, the IMAGES trial for the efficacy of intravenous magnesium in stroke) [30,31]. In the absence of a person to give emergency consent, the clinical team in England and N Ireland may randomize the patient under the Mental Capacity Act, as authorized by Berkshire Research Ethics Committee. All patients will be consented for continued participation in the trial post-operatively. Patient consent is preferred, but relatives, carers or Welfare Guardians may be approached when necessary: in situations where none of these persons are available a Consultee will be used. Trained Consultees now are available in all large hospitals.
Patients have provided consent for review of their routine clinical data for up to 5 years and for quality of life assessments at 3 and 12 months following randomization. They have not formally given signed consent for a mid-term quality of life assessment but the Chairman of the lead Research Ethics Committee for the trial has proposed that return of the mid-term quality of life assessment would imply consent**.**

***Trial documentation***
This will be kept securely at Imperial College (duplicate database at the University of Cambridge) for at least 15 years after completion of the trial.

***Planned analyses***
The analyses will be carried out according to a detailed plan drawn up before the outcome data are inspected. A CONSORT diagram will describe the patient flow and exclusions. The groups will be considered as randomised (intention to treat) as a test of the interventional policy. The primary outcome is 30-day mortality, with secondary outcomes of 24-hour, in-hospital and 1-year mortality; each will be compared with a chi squared test, and the

estimated difference in proportions accompanied by a confidence interval. Adjustment for the baseline Hardman index will be undertaken in secondary analyses using logistic regression. Time to complications, re-interventions, and major morbidities after repair of ruptured aneurysm will be compared using the log-rank test and Cox regression.
Cost-effectiveness analysis will report the mean (95% CI) incremental costs and QALYs of eEVAR versus open repair at one year, and the probability that eEVAR is cost-effective compared to open repair, at different levels of willingness to pay for a QALY gained. The analysis will address issues posed by missing EQ-5D or cost data [32] and censoring [33]. Survival analysis will be used to extrapolate any within-trial differences in costs and QALYs to project lifetime cost-effectiveness [34,35]. Sensitivity analysis will test whether the results are robust to methodological assumptions. The effect of the algorithm of care on the outcome of open surgery will be reviewed against national statistics. The statistical analysis plans will be published on the trial website before any analysis commences.

***Subgroup analyses***
A limited number of predefined subgroups will be compared using tests of interaction, only for the primary outcome (in-hospital mortality), using logistic regression. Subgroups will be defined by age (continuous), gender, and Hardman index (continuous).

***Frequency of analyses***
Since the reported experience of eEVAR comes from summation of small, selected patient series and our power calculations may be conservative, two interim analyses will be conducted for 30-day mortality after one-third and two-thirds of the planned recruitment. The principal analyses for mortality, morbidity and cost-effectiveness will be presented at the end of the trial. An independent Data Monitoring Committee will periodically scrutinize the accumulating outcome data, and advise the Trial Management Committee if safety concerns warrant a change in (or early termination of) the trial.

***Extending the generalisability of trial findings***
In the trial centres, approximately half of the patients admitted with rAAA appear to have been randomised. The reasons for non-randomisation are attributed mainly to the limited availability of interventional radiology staff/facilities and only a small minority of patients or relatives refuse consent for the trial.
To extend the generalisability of the findings or the IMPROVE trial, the trial investigators hope to access Hospital Episode Statistics data for England linked to mortality data from Data Linkage and Extract Service (formerly MRIS) to identify the outcome of all patients discharged with the diagnosis of rAAA by using anonymised records to identify surgical procedures undertaken, length of hospital stay, co-morbidities, readmissions within 12 months and survival at 12 months. It is anticipated that >60% of this cohort will have died within 12 months of admission. This renders it impossible to request consent from these non-recruited patients to access their routine NHS data. In contrast, randomised patients provide consent for this. Therefore, Health Research Authority (formerly NIGB) approval has been sought to access routine data for non-recruited patients and conditional approval obtained (Appendix IV).

It is proposed to use these HES and Data Linkage and Extract Service (DLES) data to assess overall survival outcomes (adjusted for age, gender and coded co-morbidities), the turn down rates for surgery and cost estimates of the management of rAAA by open or endovascular repair in non-recruited patients from hospitals participating in the trial. These results will be compared this with the results of randomised patients. Following discussion with DLES it has been confirmed that these data can be provided to us fully anonymised, since DLES can remove patients who have been “flagged” after randomization in IMPROVE. A flow diagram for the extended analysis is given in Appendix IV .The Audit Commission report (August 2012) estimates that the rate of routine coding errors is 9% and this will be taken into account in sensitivity analyses.

**4 *Project Timetable*** (see next page)

**5 Expertise*: Details of the trial team***
Janet Powell, Simon Thompson and Roger Greenhalgh have collaborated in previous successful trials of elective management of AAA, and have expertise respectively in AAA research & cardiovascular risk, statistics & clinical trials and vascular & endovascular surgery. Robert Hinchliffe and Bruce Braithwaite conducted the pilot trial of

endovascular versus open repair for ruptured AAA in Nottingham and will be the ethical advisers for the trial. Pre-hospital and emergency care expertise is provided by Fionna Moore (aided by Alison Walker of Yorkshire Ambulance). Taj Hassan complements the expertise in emergency care. Richard Grieve is a health economist with particular interest in emergency & critical care. Four other endovascular specialists contribute expertise to the team, Tony Nicholson in radiology, Matt Thompson (lead endovascular clinician) in design, patient algorithms & care, Nick Cheshire in use of NHS resources and training in the use of new endovascular technologies and Chee Soong, a pioneer in the use of eEVAR. In addition, critical care is represented by Simon Howell and the patient perspective by David Saunders from Nottingham. Linkage to the International Centre for Circulatory Health, registered with the UKCRN, will ensure the proper running and monitoring of the trial.
Key collaborators include many from the EVAR trials including Ray Ashleigh (Manchester) who has aided Roger Greenhalgh establish a core laboratory for reading CT scans. We also have collaborators in all the non-applicant participating centres: Newcastle, Professor M Wyatt; Manchester, Professor C McCollum/ Dr R Ashleigh; Hull, Mr I Chetter; Cambridge, Mr J Boyle; Royal Free, Ms M Davis; St Thomas's Ms R Bell/Mr P Taylor; Bournemouth, Mr S Parvin.

**6 Service users**

We have involved service users (n=7) in the design of the trial. We used the patient information pack and part of the questionnaire that has been developed and validated in collaborative research with the Picker Institute (for a project on elective repair of AAA) as a basis for in-depth interviews to identify patient perspectives on trial design and outcomes. We have identified one service user, Anne Cheetham, wife of a survivor of ruptured aneurysm repair, sits on the Trial Steering Committee.

***Project timetable***

| Activity | **IMPROVE trial** timelines | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Quarter | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1-2 | 1-4 | 1-2 |
| Year | 2009 | | | 2010 | | | | 2011 | | | | 2012 | | | | 2013 | | | | 14 | 2015 | 2016 |
| *IRAS* | | | | | | | | | | | | | | | | | | | | | | |
| *Recruit staff* | | | | | | | | | | | | | | | | | | | | | | |
| *Establish committees* | | | | | | | | | | | | | | | | | | | | | | |
| *Approving UK centres* | | | | | | | | | | | | | | | | | | | | | | |
| *Centre credentials* | | | | | | | | | | | | | | | | | | | | | | |
| *Randomisation service* | | On going | | | | | | | | | | | | | | | | | | | | |
| *Trial web site* | | | | | www.improvetrial.org ongoing | | | | | | | | | | | | | | | | | |
| *Early recruitment* | | n=30 | | | | | | | | | | | | | | | | | | | | |
| *Main recruitment* | | | | | | | | | | | | | | | | | | | | | | |
| *Patient follow up* | | | | | | | | | | | | | | | | | | | | | | |
| *Participant meetings* | | 1 | | | | 2 | | | | 3 | | | | | 4 | | | | 5 | | | |
| *European centres start* | | | | | | | | | | | | | | | | | | | | | | |
| *Data monitoring* | | ....50 | | | | | | | 200 | | | | 400 | | | | | | | | | |
| DLES ~~*MRIS*~~ *flagging* | | | | | | | | | | | | | | | | | | | | | | |
| *Interim analyses* | | | | | | | | | | 1 | | | | | 2 | | | | | | | |
| *30d mortality available* | | | | | | | | | | | | | | | | | | | V S | | | |
| *Data cleaning* | | | | | | | | | | | | | | | | | | | | | | |
| *Statistical analysis plans* | | | | | | | | | | | | | | | | | | | | | | |
| *Lock database* | | | | | | | | | | | | | | | | | | | | | | |
| *Data analysis* | | | | | | | | | | | | | | | | | | | | | | |
| *Main results to committees* | | | | | | | | | | | | | | | | | | | | | | |
| *Draft manuscript(s)* | | | | | | | | | | | | | | | | | | | | | | |
| *HTA report & final results* | | | | | | | | | | | | | | | | | | | | | | |
| Legend | Set up completed | | | | | | | Intense activity | | | | | | | | Low intensity activity | | | | | | |
| | Very intensive activity | | | | | | | completion | | | | | | | | | | | | | | |

VS 30-day mortality results presented to investigators at Vascular Society November 2013

***7* Justification of support requested**

Research support The support requested is for the research costs, including staffing and research costs to the participating centres. The use of the novel technology, eEVAR may be associated with cost savings because of shorter stays in critical care and hospital beds [8,36]. The collection of clinical data and monitoring of this data is onerous and will be a research cost enabled by adding time to the current EVAR trial co-ordinators, listed in references 15,16. Each participating centre will receive up to £5000 to support local research infrastructure and then £325 per patient randomized (£225 for the in-hospital data and audit and £50 each for 3m , 1y and mid-term follow-ups).

The trial manager (supervised by Professors Powell, Thompson & the International Centre for Circulatory Health) will be responsible for checking centre eligibility, facilitating approvals at each participating centre, chasing missing data and monitoring data and compliance with the consent process, as well as working with the local trial co-ordinator and nominated clinicians, to ensure the on-going training available for rotating staff. The role of part-time statistician (supervised by Professor S Thompson), who will be involved in all aspects of the trial including preparing interim reports for committees and final data analysis and part-time health economist (supervised by Dr R Grieve) to focus on the cost-effectiveness aspects of the trial, including final analysis and data-modeling, may be combined with the appointment of Lois Kim (previous experience in both roles from the MRC supported MASS trial [14]). Office, publication and travel costs are necessary to support all staff and the principal investigator. Randomisation and web-based data capture will be conducted through thesealedenvelope.com. The Trial Manager will deliver training on web-based data capture and the taking of consent during the site initiation visit, which will take place once local approval has been granted. R Hinchliffe and B Braithwaite will deliver aspects of organizational training for eEVAR. All CT scans (anticipate 650) will be read in a core laboratory (already established at Imperial College by Professor Greenhalgh) at £40 per scan and patients leaving hospital alive will be flagged for date and cause of death with the NHS Information Centre. Travel costs are necessary to underpin committee and participant meetings and the for the trial manager to visit the trial centres to monitor data quality. In the final 6 months of the project secretarial help is requested to facilitate the timely delivery of manuscripts and reports.

NHS support costs

There may be very minor NHS costs accrued from a policy of diverting ambulances to the large vascular centres (where this trial will take place), but this is a policy already in effect in the large metropolitan (e.g. London, West Yorkshire) and many other areas (e.g. Dorset). The costs of obtaining patient consent have been listed as an NHS support cost.

Treatment costs The treatment costs are based on the published costs for ruptured aneurysm [36,37], the costs for acute treatment of AAA by either open or endovascular repair [8], the costs of the principal components of care taken from elective procedure [15] and the mean number of days for intensive care and hospital stay taken from UK data and Cochrane reviews, all updated to 2008-9 values [9,36]. The Cochrane review shows that the procedure time (use of operating theatre) is shorter for endovascular repair and that the time on intensive care is reduced to a mean of 2 days (versus 5.2 days for open repair) [8,23]. Similarly endovascular repair is associated with a reduced usage of blood products and length of ward stay. Treatment costs have been estimated for 200 patients undergoing endovascular repair versus 400 undergoing open repair (300 randomised to open repair and 100 not anatomically suitable for eEVAR). Endovascular repair has higher procedure costs, which includes the endografts and higher reintervention costs. On average open repair is a associated with increased time in the operating theatre, increased administration of blood products, increased usage of critical care and vascular surgery ward beds, so that overall this may be the more expensive option, in concordance with published data [8,36]. In the Netherlands the hospital costs of endovascular repair have been estimated recently at 17000€ versus 21000€ for open repair [36]. These values are similar to our listed costs of £15,000 for endovascular repair and £15,700 for open repair, which includes the follow up to 1 year.

However, the is trial is likely to place an added burden on intensive care facilities in the participating hospitals, much of this as a result of the 1:1 randomisation (which increases the number of patients undergoing open repair). Additional central support for Critical care usage, in excess of £500,000, may be necessary.

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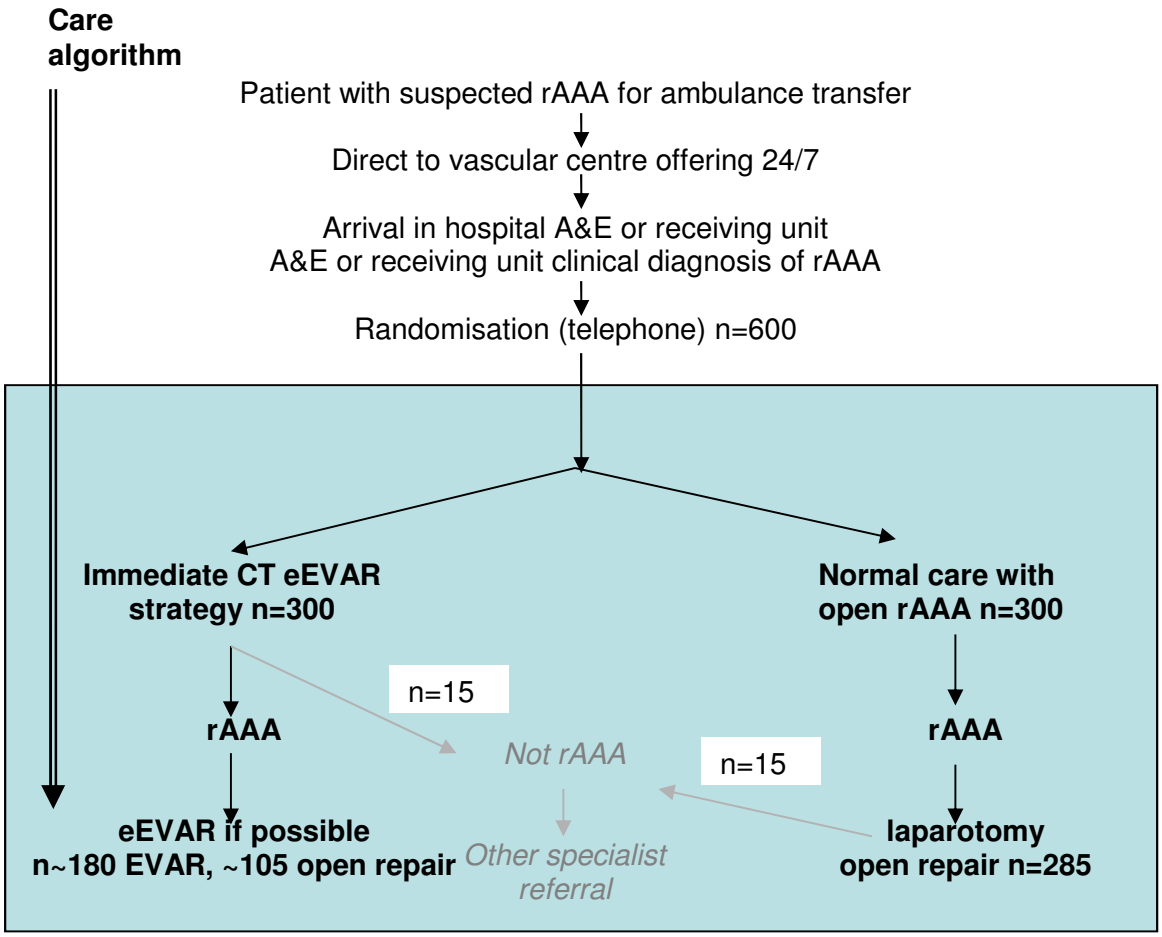
**9: Flow diagram of trial (Figure 1)**




Primary end point 30-day mortality
Secondary endpoints: 24h, in-hospital & 1y mortality, major morbidities, re-interventions, costs, cost-effectiveness modeling and 3y cost-effectiveness modeling.

**APPENDIX 1**: **Tables**

Table 1 Potential annual recruitment to ruptured AAA trial, from audits 2008-2009

| | |
|---|---|
| Belfast | 35 |
| Newcastle | 40 |
| Liverpool | 40 |
| Manchester | 40 |
| Leeds | 45 |
| Hull | 20 |
| Nottingham | 50 |
| Leicester | 30 |
| Birmingham | 30 |
| Cambridge | 30 |
| Royal Free London | 20 |
| Royal London | 20 |
| St Thomas's, London | 30 |
| St George's London | 20 |
| Imperial, London | 20 |
| Portsmouth | 35 |
| Bournemouth | 30 |
| Other possible centres: e.g.Truro, Sheffield | c.100 |
| | Potential annual recruitment from 500 patients, allowing for 20-25% loss of patients for operational reasons<br><br>Planned recruitment is up to 320 patients/pa |

Table 2 Reasons for non-randomisation in the Nottingham study

| Reasons for non-randomisation | Number of open operations | Survived to 30d |
|---|---|---|
| Haemodynamic instability | 4 | 0 |
| No endovascular team | 3 | 1 |
| Ruptured AAA discovered at laparotomy for other pathology | 1 | 0 |
| Ruptured night before scheduled open repair (contained rupture transferred in night) | 1 | 0 |
| Aneurysm morphology unsuitable for EVAR (known AAA awaiting open repair as unsuitable morphology for EVAR) | 1 | 0 |
| Surgeon preference | 3 | 1 |

**APPENDIX II: Algorithm and protocols for patient care**

1 ***Integrated care prehospital and Accident & Emergency strategy***

The pre-hospital care and Emergency Department (ED) management of patients with suspected AAA rupture are a key component to producing an optimal overall outcome. The eEVAR study will ensure that in a multi-centre trial of this nature these parts of the process produce a consistent quality assured standard of care delivery in conjunction with robust methodological procedures for gaining consent to recruitment to the trial. In addition, we will use standardised processes for study documentation, education and quality assurance. These are described in greater detail below.

The pre-hospital component will ensure that wherever possible all patients with suspected AAA are managed using standardised national guidance for the assessment and management of such cases, based on the abdominal trauma guidelines [17]. Particular attention will be paid to having a consistent rapid process of assessment with key 'red flags' suggesting that a patient might be suffering from an AAA rupture. Once a diagnosis is suspected the need for rapid transfer to an ED is part of national guidance. In addition, there are guidelines on the appropriate usage of intravenous fluids in such circumstances and to ensure that fluids are withheld unless cerebral perfusion is compromised and then used only judiciously. A quality assurance matrix for adherence to the trial protocol will be developed that monitors key markers of the assessment process, transfer timelines and usage of pre-hospital interventions. This will allow ease of feedback to pre-hospital care personnel.

In the ED at recruiting centres, there will be a nominated clinician responsible for maintaining standardised integrated care pathways (ICPs). These will ensure that the assessment process is allowed to be rapid (due to the nature of the pathology) and with clear documentation of the various components of the process. Standardised investigation panels will be incorporated into the ICPs to ensure clarity and minimise any time delays. In some units the assessment process will be supplemented with a bedside ultrasound performed by ED medical staff. The ICPs will also contain all relevant study documentation (including the information and consent forms) for patients, their relatives or advocates as appropriate. This will also ensure a high level of quality in the overall delivery of care as well as key aspects of research governance and especially consent in a sometimes fraught ED environment with a patient suffering from a potential immediate life threatening illness. The ICP will also ensure that a high quality handover to the Vascular Intervention team.

Consistency of care in the various components of the study pathway in the pre-hospital and ED setting is critical to the project. It is important to note that these processes will be significantly strengthened with a high quality educational strategy and communications system for feedback. These standard educational strategies will be supplemented with a web based communication platform and eLearning modules. This approach will enhance interactivity for all staff involved in the trial as well as track uptake of key educational messages in individual trial centres.

2 ***eEVAR protocol for pre-operative CT scanning and assessment***

1 Fitness for CT to be assessed by interventional team before transfer to CT. When the vascular team is contacted about a patient in another hospital with a suspected rupture, the patient should be transferred to the centre rather than wait for a scan to be organised locally. When a patient is being transferred from another hospital for CT, the CT team should be available as soon as the patient arrives at the receiving centre.

2 Contrast enhanced scan to be taken from the level of the diaphragmatic hiatus to lower border of femoral heads. The scan must be performed during the arterial phase of contrast enhancement. The exact protocol will depend on the scanner available and the individual department but a contrast dose of 100ml given at 3-4ml/second is recommended. The notional slice thickness should be 1-2mm. When a scan already was performed at another hospital, the patient is to transfer to the trial centre with a CD copy of the scan (DICOM data). Ideally 2 copies will be provided, one for the trial core lab. *Randomisation must occur before review of the CT scan provided.* Repeat CT scans should be avoided.

3 All CT scans must be reviewed by the interventional team for diagnosis and measurement.

4 Definition of rupture is intraperitoneal or retroperitoneal blood seen outside the aneurysm sac.

5 Anonymised CD containing DICOM data of the scan to be sent to the trial centre for core laboratory analysis.

*Assessment of suitability for eEVAR*

The proposed trial is pragmatic and it is therefore not possible to set exact criteria for anatomical suitability for endovascular repair of ruptured AAA. The criteria will vary to a marginal degree from centre to centre and will be based on experience, type of graft preferred, the configuration of graft, the development of new technologies and other local factors. In general, the anatomic considerations are similar to those for elective procedures and proximal neck morphology with a diameter exceeding 32mm or a length less that 10mm may be considered unfavorable, although there will be no absolute requirements set for the proposed study. Iliac artery diameters should be in the range 8-22mm.

*Technical assessment of procedure success*

One contrast enhance dual phase (arterial and venous) scan should be performed 3 months post implant. Scan volume should be from the diaphragms to the lower border of the femoral heads. A CD of the DICOM data should be sent to the core lab for analysis.

### 3 *Protocol for eEVAR implantation*

Again, the protocol for eEVAR will be set locally and protocols will be available to the trial management committee. Several variables associated with eEVAR will require documentation. These will include: (a) Location of procedure (operating theatre / angiography suite / hybrid); (b) Type of anaesthesia; (c) Configuration and make of endograft; (d) Access (cut down or percutaneous); (e) Use of occlusion balloon; (f) Requirement for adjunctive radiological or surgical procedures.

### *4 Anaesthetic algorithms*

There will be a nominated anaesthetist in each centre, with responsibility of ensuring standards of care. Patients with a ruptured AAA may suffer dramatic cardiovascular decompensation at induction of general of anaesthesia. Anaesthetic agents may cause profound hypotension when given to patients with hypovolaemia. Positive pressure ventilation reduces venous return. The loss of abdominal muscle tone associated with the induction of general anaesthesia may result in a contained rupture becoming an intraperitoneal haemorrhage. Anaesthetic guidelines for both groups will be designed to manage these risks.

Both groups: Until the rupture has been controlled by aortic cross clamping or stent graft deployment fluid resuscitation, will be restricted to that required to maintain a systolic blood pressure of 80 mmHg or to maintain adequate cerebral and myocardial perfusion. Once control has been achieved the patient will be vigorously fluid resuscitated. Blood (products) will be given as indicated during the procedure and red blood cell salvage will be used where available. Patients will receive intensive care or high-dependency care as deemed clinically appropriate. Fluid resuscitation will be continued into the postoperative period until the patient has a stable and adequate blood pressure and an adequate urine output and the patient is normothermic.

eEVAR group: Stent-graft placement preferably will be performed under infiltration anaesthesia of the groins to obviate the risks of cardiovascular decompensation from induction of general anaesthesia in the presence of a ruptured aneurysm. Once an endograft has been successfully deployed and/or the rupture is successfully controlled the patient will be fluid resuscitated and general anaesthesia can be introduced for other procedures as necessary, e.g. a femoral-femoral crossover graft for aorto-uni-iliac devices. It has been the experience of the Nottingham group [9] that patients frequently do not tolerate this latter procedure under local anaesthesia because of pain from lower limb ischaemia.

Open repair group: Anaesthetic management of patients will require induction of general anaesthesia before aortic cross-clamping. Vasopressors and, if necessary, adrenaline will be used to maintain an adequate blood pressure until a cross clamp is placed. Heparin will not be administered as patients generally have a degree of coagulopathy.

Appendix III

## *The following information sheet is to be read to the patient in England & Northern Ireland*

You have a life-threatening condition where a major blood vessel has burst in your tummy. You need major surgery (an operation) on your tummy to repair the blood vessel and try to save your life.

*Pause for the patient to respond*

There are two methods of doing this operation. The standard method involves cutting open your tummy and replacing the burst blood vessel.
The second is a new 'keyhole' technique that involves re-lining the bleeding blood vessel through the artery in your groin: this requires a special X-ray scan first and may lead to a slight delay with this treatment.

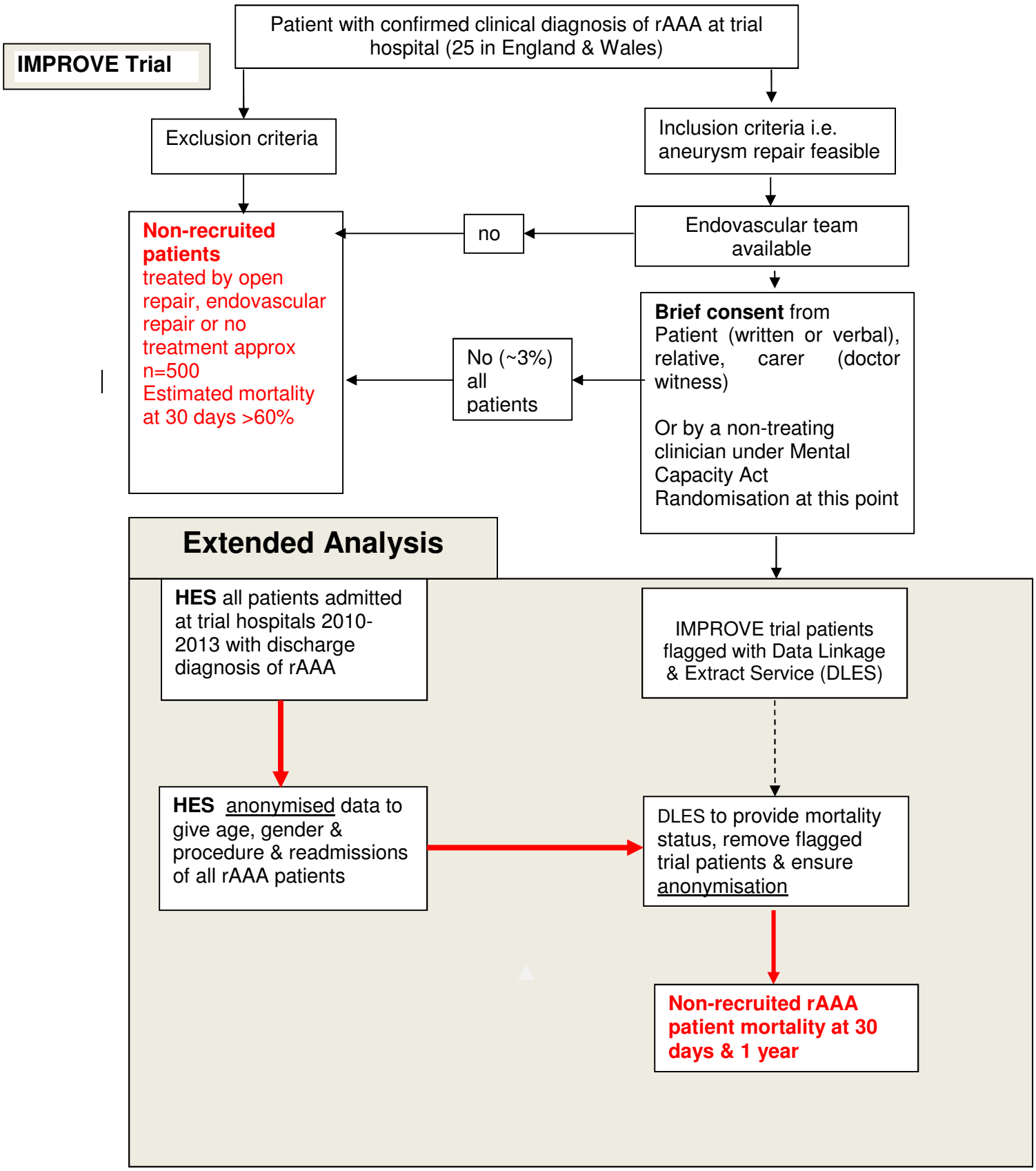
We do not know which treatment is best. So, we would like your permission to enter you in to a trial where we choose at random which operation you have.

The urgency of the situation means that we will discuss in detail what has happened after your operation.

You are under no obligation to take part in this study. If you decline, your care will not be compromised and you probably will have the standard open operation rather than the new treatment.

Appendix IV

## Generalisability of the IMPROVE trial



NIGB
Ethics and Confidentiality Committee
On behalf of the Secretary of State for Health

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Professor Janet Powell
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11 September 2012

Dear Professor Powell

**REPLACEMENT ECC 4-03 f)/2012 Emergency endovascular aneurysm repair: IMPROVE trial.**

Thank you for your application for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality. The role of the NIGB Ethics and Confidentiality Committee (ECC) is to review applications submitted under these Regulations and to provide advice to the Secretary of State for Health (SofS) on whether an application should be approved, and if so, any relevant conditions. This application was originally considered on 19 July 2012.

Following subsequent requests for clarification from the applicant and Chair of the research ethics committee, the decision has been discussed with the Chair who led on this application, and a revised provisional outcome letter issued. **This replaces the provisional outcome letter dated 01 August 2012.**

**Secretary of State decision**

Following consideration of the ECC advice, reproduced below, the Secretary of State has determined that the following aspects of the application are approved under the Regulations:

1. Access to MRIS data and cause of death for specified patients within the IMPROVE trial who have not been able to provide second post-operative consent and are deceased.

2. In relation to non-randomised patients (all patients admitted with a diagnosis of ruptured abdominal aortic aneurysm (rAAA) to IMPROVE Trial hospitals during the randomisation period of 2010 – 2013), an anonymised dataset to be provided from HES and MRIS to the applicant.

ECC advice

The ECC noted that the principle research question of this randomised clinical trial was to identify whether a strategy of preferential endovascular repair of ruptured abdominal aortic aneurysm,

NIGB

Ethics and Confidentiality Committee
On behalf of the Secretary of State for Health

versus the current practice of open surgical repair, would significantly reduce the 30 day mortality of the condition. A total of 600 patients would be randomised into the trial, and these would be patients who had an in-hospital diagnosis of ruptured abdominal aortic aneurysm. These would initially be approached and recruited into the Trial by clinicians from emergency care or vascular teams; in line with the Mental Capacity Act where applicable. Member advice on the two aspects of the application is specified below:

1. Access to MRIS data where the patient has not provided the second post-operative consent

The first aspect sought support under the Regulations to continue to access mortality data for a sub-cohort of the randomised patients. Members noted that these patients would have provided consent for randomisation into the IMPROVE trial, but because of the emergency circumstances these patients would not have provided specific consent for the access to NHS data sources.

As a whole, members agreed that where the patient was deceased, then it would be appropriate to recommend support for the purposes of continued flagging.

2. Access to non-randomised patient information

The second aspect sought anonymised information on non-randomised patients (those not randomised in the IMPROVE trial). The purpose of this aspect was to enable the comparison of survival of patients in and outside of the IMPROVE trial, so as to enhance the generalisability of the trial findings.

It was understood that in order to receive information on the non-randomised patients, this would involve the Health and Social Care Information Centre (HSCIC) processing confidential patient information of the non-randomised patients, in order to link and subsequently provide an anonymised dataset on this sub-group to the research team. Therefore, while the research team would not require a recommendation of support under these Regulations to receive an anonymised dataset, the aspect of the HSCIC processing the data on behalf of the researcher would fall within the remit of the support and it is this aspect to which support would apply.

It was noted that the researcher would receive an anonymised data set for non-randomised patients and this would consist of anonymised mortality data from HES/MRIS, so that the primary trial outcome of 30-day mortality could be compared in trial and non-trial patients, and this would be grouped by age band, gender and type of intervention performed.

In terms of debating whether consent would be feasible, members noted the desired outcome to identify the outcomes of all patients admitted with a diagnosis of rAAA through using anonymised records to identify surgical procedures undertaken, length of hospital stay, co-morbidities, readmissions with and survival at 12 months. In particular, the application indicated that over 60% of this cohort would likely to be deceased. Members therefore agreed that for this sub-cohort, consent would not be generally feasible for this aspect.

Members agreed that the outcomes would have a public benefit as the condition incurred a high mortality rate, and that consent would be sought where feasible. There was a clear medical purpose and the use of identifiers reasonable and proportionate. As such, the committee advised the Secretary of State for Health that the application be approved, in line with these comments.

National Information Governance Board for Health and Social Care

NIGB

Ethics and Confidentiality Committee
On behalf of the Secretary of State for Health

**Specific conditions of support**

1. Security assurance. Please note there has been a change to the security review process. Please review the following link (http://www.nigb.nhs.uk/s251/forms) which sets out the change, and please follow the guidance given. It is understood that contact has been made with this team, and that the NIGB ECC will require confirmation from the security team when the assessment is satisfactory.

2. A favourable REC opinion

**Further actions**

When available, please provide a copy of the favourable REC opinion. Once received, and once we receive confirmation that the security arrangements are satisfactory, a final approval letter will be issued.

Please do not hesitate to contact me if you have any queries following this letter, ensuring you quote the above reference number in all future correspondence.

Yours sincerely

Natasha Dunkley
NIGB Approvals Manager

National Information Governance Board for Health and Social Care