CLINICAL STUDY PROTOCOL

Study Title:	An evaluation of the effect of an angiotensin-converting enzyme (ACE) inhibitor on the growth rate of small abdominal aortic aneurysms
ACRONYM:	**AARDVARK** **Aortic Aneurysmal Regression of Dilation :** **Value of Ace-inhibition on RisK**
Protocol Number:	CRO 1644
Ethics Reference:	**10/H0711/80.**
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I BACKGROUND AND RATIONALE

(i) Background

There is no clear, consistent evidence in favour of ACE-inhibitors slowing AAA growth rates and it is not known how well patients with small AAAs tolerate ACE-inhibitors. Previous trials of other drugs to slow AAA growth have been hindered by poor patient compliance. Therefore a pilot trial is proposed, to assess whether ACE-inhibitors slow AAA growth and are well tolerated in doing so.

(ii) Existing Research

A Cochrane review of the four trials of screening for abdominal aortic aneurysm (AAA) summarises the benefits for screening to reduce aneurysm-related mortality in older men (1). In addition, the later 7 year report from the MASS trial (screening trial based in the South of England) has suggested that screening may be associated with a benefit in all-cause mortality (2). With this persuasive evidence, in favour of aneurysm screening, the National Screening Committee has recommended that screening for AAA, using ultrasonography, is available for all men in the UK at the age of 65 years (3). National Aneurysm Screening will be implemented in a progressive manner during the period 2009-15. The small, asymptomatic aneurysms (3.0 to 5.5 cm in diameter) will be followed up in the screening programme and patients only referred for surgery when the aneurysm reaches 5.5 cm diameter. Since the natural history of these small aneurysms is progressive enlargement in the majority of cases, there is an urgency to identify a safe medical therapy to limit aneurysm growth and limit the number of patients eventually requiring aneurysm repair.

Most of the aneurysms (80-90%) detected in population screening programmes are small, between 3.0 and 5.5cm in diameter (4). Evidence from four randomised trials has shown that surveillance (rather than open repair or EVAR) is a safe and less costly management policy for these small aneurysms, with the rupture rate in men being <1% per annum (5-8). Therefore, National Aneurysm Screening also will offer regular ultrasonographic aneurysm surveillance to those men identified with small AAA. When the aneurysm diameter reaches 5.5 cm, usual policy is for intervention with either endovascular or open aneurysm repair, although the mortality associated with these procedures is in the range of 2-6%.

The identification of medical therapies to limit aneurysm growth is likely to enhance both patient survival and the cost-effectiveness of aneurysm screening programmes.

The rate at which small aneurysms grow is highly variable, although the average is 2.6mm/y, and the time taken to reach the 5.5 cm diameter threshold depends on the size of the aneurysm at detection, Figure 1 (9). Currently, only two types of drugs have been tested for their efficacy in decreasing aneurysm growth rates: β-blockers and antibiotics. There is no convincing evidence that either of these drug classes was effective (10, 11). Observational studies have reported on efficacy of several other classes of drug to decrease AAA growth rates: systematic review and meta-analysis suggests that statins may be effective. In this recent systematic review, there was no evidence that anti-hypertensive drugs, including ACE-inhibitors were effective (12). The influence of ACE-inhibitors on small aneurysm growth rate among nearly 2000 patients enrolled in the UK Small Aneurysm Study and Trial has been assessed (13). Among these patients, the use of ACE-inhibitors at baseline was associated with a small, but significant increase in aneurysm growth rates, this significant difference remained after adjustment for known confounders eg. smoking, diabetes, blood pressure and peripheral atherosclerosis. However, since this evidence comes from non-randomised data it remains subject to bias and unrecognized confounders.

In contrast, in 2006, a large, retrospective, Canadian study reported that current use of ACE-inhibitors, compared with any other anti-hypertensive agent, was associated with a reduced incidence (by 20%) of aortic aneurysm rupture and the authors speculated that ACE-inhibitors would reduce the growth rate of

small AAAs (14). There are several problems associated with a study of this nature, particularly unrecognized confounders such as smoking, blood pressure control and poor access to health care. In particular, smoking is a risk factor for AAA rupture and increases aneurysm growth rate and smokers are more likely to suffer the cough induced by ACE-inhibitors and hence are less likely to tolerate and therefore take ACE-inhibitor therapy. Also there is some evidence that higher mean blood pressure (BP) increases the risk of aneurysm rupture (15).

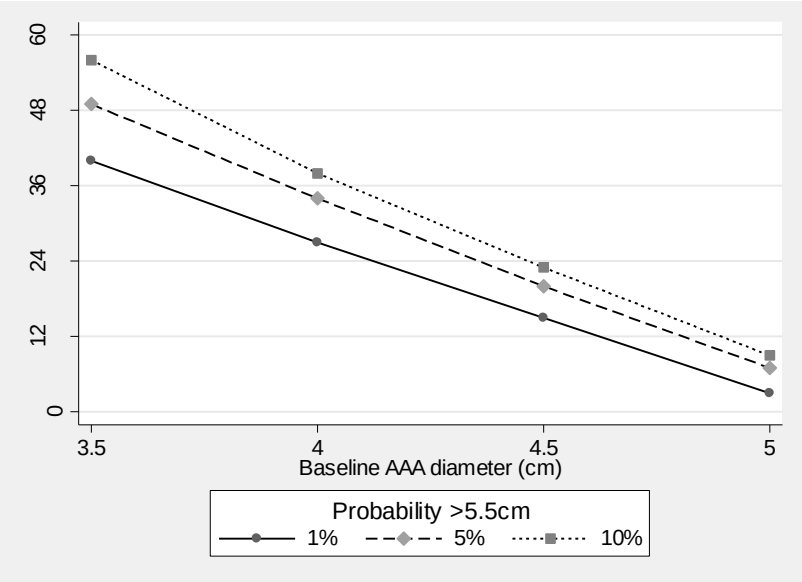
The strongest evidence associating the renin-angiotensin system with AAA comes from experimental studies. Both angiotensinogen and the angiotensin type1 receptors (AT1) are upregulated about 2-fold in the aortic wall of AAA versus the wall of atherosclerotic aorta, although the expression of the AT2 receptor was similar (16). The presence of the 1166C polymorphism in the AT1 receptor predisposes to the development of AAA (17) and in hypercholesterolaemic mice, angiotensin II infusion induces experimental aortic aneurysms, which can be prevented with use of ACE-inhibitors (18).

Nevertheless there is no reliable evidence that either ACE-inhibitors or blood pressure lowering slow the progression of small AAA in man. A previous randomised trial of propanolol versus placebo in patients with small AAA did report a small but significant reduction in diastolic blood pressure in the propanolol versus placebo group: aneurysm growth rates were non-significantly lower in propanolol group (10). However, this trial suffered from the high percentage of patients discontinuing treatment, particularly in the propanolol group where 42% patients discontinued their medication early. Furthermore beta-blockers are thought to be less effective at reducing central blood pressure compared with other antihypertensive agents, including ACE-inhibitors. Small trials of other drugs (e.g. doxycycline) to slow AAA growth also have reported significant early discontinuation of active treatments. Tolerance of ACE-inhibitors in patients with small AAA is unknown, Since smoking is the strongest known risk factor for AAA, many of those with small AAA are likely to have lung dysfunction and a smokers cough and their tolerance of ACE-inhibition in this setting is still to be established.

Other trials underway

Searching of clinical trial data-bases (ClinicalTrials.gov and Controlled-trials.com) has not shown any trials of ACE-inhibitors in AAA. A feasibility study of doxycycline versus placebo has been completed in the USA and the investigators now plan to enrol 250 patients with small AAA randomised to either doxycycline 20 mg daily or placebo, with 2 year follow up anticipated to show a 40% reduction in aneurysm growth rate in the doxycycline group (personal information from the principal investigator BT Baxter, Omaha, Nebraska).

Figure 1



Reasons for undertaking a Pilot Feasibility Trial

The compliance of patients in previous trials of drugs to limit aneurysm growth rates has been poor. For example, in one of the propanolol trials 42% of patients stopped their active trial medication early, as did 25% of the placebo patients (19). The compliance with ACE-inhibitors in this population with extensive smoking histories is uncertain.

Aneurysm growth rates for those taking ACE-inhibitors at baseline (9% of 1698 patients with AAA3.0-5.5cm diameter) in the UK Small Aneurysm Trial and Study have been investigated (13). Both crude and adjusted growth rates were significantly higher in patients taking ACE-inhibitors, about 10% higher. Furthermore, ACE-inhibitors had no protective effect on aneurysm rupture in this cohort. These observational data on growth rates (and rupture) conflict with the large Canadian observational study [9] and a much smaller study of only 25 patients showing a 75% reduction in aneurysm growth rates for those taking ACE-inhibitors in the Huntingdon Screening Study (20). Therefore, the data on benefits of ACE-inhibition on aneurysm growth rates are inconsistent and uncertain.

Risks and anticipated benefits for trial participants

The specific ethical issues relevant to this trial relate to:

Drug administration:

a) *Angiotensin Converting Enzyme – Inhibitor* (perindopril 10mg). The commonest side effect associated with ACE-inhibitors is a dry cough. Patients experiencing a new-onset persistent dry cough that is intolerable will be told to stop the drug for 2 weeks. If the cough resolves with drug cessation, the subject will be switched to an angiotensin-receptor blocker, (losartan 100mgs, that has a lower incidence of cough compared with ACE-Inhibitors) and will continue in the trial on this agent. The administration of perindopril in the dose suggested above should only lower the systolic blood pressure (SBP) by approximately 6 mmHg and diastolic blood pressure (DBP) by 4mmHg. This should have minimal effects on the subjects enrolled in this study. We have chosen to use perindopril, rather than other ACE-inhibitors, because it is generic and has been evaluated in several large Registered Clinical Trials and has been shown to have important cardiovascular benefits (21-24).

   *b) Dihydropyridine Calcium channel blockade (*amlodipine 5mg*).* The commonest side effect with this type of calcium channel blockers is ankle oedema. The dose of calcium channel blocker used in this trial (amlodipine 5mg) is expected to lower the SBP by 6mmHg and DBP by 4mmHg and thereby match that produced by perindopril.

   c) Placebo

   This is an inert tablet which carries no side-effects or risks but which if anything is beneficial to the participants. It will allow the impact of the BP lowering effect by other agents to be evaluated.

Ultrasound scans:

The ultrasound examination is not associated with any increased risk to the patient in the presence of an aneurysm. For patients with aneurysms <4.5 cm in diameter there will be an increased frequency of ultrasound examinations, but benefits of more regular scans may include earlier detection of rapidly growing aneurysms or detection of aneurysms that have reached a size that mandates treatment.

Financial cost:

There will be reimbursement to patients for travel associated with the trial.

II OBJECTIVES

1 To investigate the hypothesis that an ACE-inhibitor reduces abdominal aortic aneurysm (AAA) growth rate in a 3-arm randomised controlled pilot trial: The three interventions are ACE-inhibition with perindopril versus equivalent blood pressure reduction with amlodipine (a calcium channel blocker) versus placebo. By comparing the effects in the perindopril and amlodipine arms, this design will permit an evaluation of any BP independent effects of perindopril.

2 Pending results of the pilot trial, to work with the local and National Aneurysm Screening programme to conduct a larger, definitive 3-arm randomised controlled trial, to investigate the hypothesis that BP reduction with an ACE-inhibitor slows the rate of small AAA growth preferentially compared with other antihypertensive agents. Aneurysm-related mortality, morbidity and quality of life will be the major secondary end-points.

III STUDY DESCRIPTION

III A Design

This study will be performed at investigational sites in the UK. This is a randomised, single-blind, multicentre, placebo-controlled study in participants with an SBP <150mmHg either untreated or on treatment with certain pre-specified background anti-hypertensive medications. The pilot trial will have 3 arms, with patients being randomised to either perindopril (10mgs arginine salt daily) or placebo (primary comparison) or amlodipine (5mgs daily) (secondary comparison). The perindopril and amlodipine doses will have similar effects on blood pressure reduction and hence the secondary comparison will help to inform whether all/any benefits of perindopril are independent of BP reduction. The pilot trial is designed to inform a larger, definitive trial of patients identified in the National Aneurysm Screening programme, after 2012-3 when screening should be active in more than half the population of the UK.

III B Treatment regimens

Planned interventions and measurements

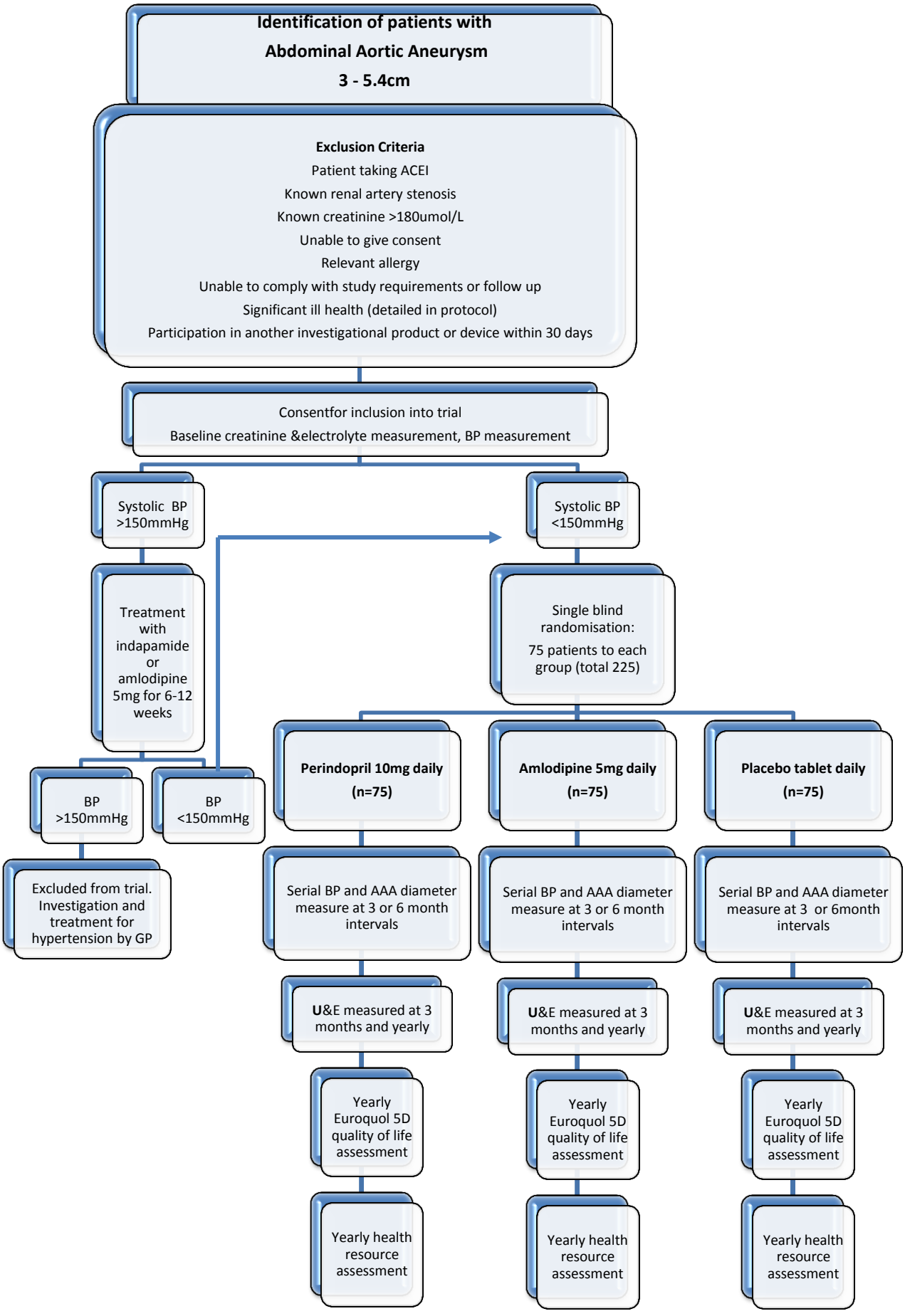
The primary comparison is the effect of AAA growth in association with ACE-inhibition compared with placebo and hence one third of randomised patients will receive perindopril 10mg daily and one third will receive placebo. Additional blood pressure lowering medication will be added if the SBP is >150mmHg at screening in the form of indapamide SR 1.5mgs daily or if this is not appropriate then amlodipine 5mg.

In order to evaluate the BP-independent effect of ACE-inhibitors, it is proposed to lower BP to a similar degree as achieved on perindopril 10mg by randomising one third of patients to a calcium channel blocker (amlodipine 5mg daily.). It is estimated that at these doses the two drugs will produce similar average BP-lowering effects of about 6/4mmHg in what is an elderly population. Both drugs can also be compared with placebo to evaluate a BP-lowering impact on AAA growth.

The most common side-effect of ACE-inhibitors is cough affecting about 15% of those treated. However pre-trial screening of those with a history of ACE intolerance will reduce the incidence of this problem. This side effect will be monitored, particularly since nearly all AAA patients will be smokers or ex-smokers who tend to tolerate ACE-inhibitors less well. Where cough is persistent and intolerable, the patients will stop medication for 2 weeks and if the cough lessens they will be changed to the angiotensin receptor blocker (ARB), losartan (100 mg per day).

A recent systematic review found that statin use was associated with reduced growth rates of AAA (12) and since AAA can be considered as a “CHD equivalent” in terms of cardiovascular risk, statin therapy is recommended for all patients with a small AAA. Consequently for all patients recruited into the trial, who are not currently receiving a statin, this therapy will be initiated via a request for the patients’ general practitioner to prescribe a drug in this class

Flow diagram of trial (Figure 1)



III C Study population

Frequency and duration of follow-up

Depending on the size of the AAA the frequency of follow-up recommended in guidelines varies between 3 to 12 months. However to improve the modelling of aneurysm growth rate and for simplicity, all patients will be screened on a 3 or 6 monthly basis (this frequency will be decided by the patient and/or the site)For those that opt to undertaken 6 monthly visits, the following visits must be undertaken – screening, baseline (0 months), 3 month, either 6 or 9 month, 12 month, 18 month and 24 month visits.

Follow up will be for 24 months for all patients. Since it is anticipated that this pilot trial may stimulate a larger, definitive trial, arrangements will be put in place, with our NHS colleagues, to continue patient follow-up after the active pilot trial follow up.

III D Sample size and power considerations

(i) Sample size

Based on the inclusion of 225 patients with a baseline AAA of <5.5cm diameter, and estimated growth rates (based on UKSAT and UKSAS (9)) of 2.6 (SD 1.8) mm/year the trial will have 90% power at the 5% level to detect a 38% reduction in growth rate (similar to the effect size being evaluated in the doxycycline trial) associated with the ACE-inhibitor compared with placebo. The detectable reduction in growth rates with 80% and 70% power are 31% and 28% respectively. On the assumption that the effects on aneurysm progression are specific to ACE inhibitors rather than other anti-hypertensive drugs, the trial has power to detect a smaller difference in growth rate (<20%) by comparing the ACE inhibitor group with the other 2 groups. These calculations allow for a 10% drop out or inadequate ultrasound data to estimate the growth rate.

The AAA growth rate in the amlodipine group will allow an evaluation of the extent to which the ACE-inhibitor effect is attributable to BP reduction. The events of aneurysm repair, aneurysm rupture and death will be documented and patients censored at these time points or at the end of the study. Over a 2 year follow-up period, a total attrition rate of 10% has been included in the power calculations for the trial.

Patient compliance Patient compliance with perindopril and potential side effects of drug treatment will be monitored closely. Patients who develop a persistent and troublesome cough proved to be due to treatment with the ACE-inhibitor will be switched to an angiotensin II antagonist (ARB) losartan 100mgs. They will continue in the trial and be followed up on an intention-to-treat basis. To encourage continued involvement in the trial, retention techniques (follow-up phone-calls, birthday and Christmas cards) may be used. Compliance with study medication will be evaluated using pill counts.

IV EXPERIMENTAL METHODS

IV A Subject selection

(i) Inclusion criteria

- Willing and able to give written informed consent **AND**
- Men or women, aged at least 55 years, **AND**
- With AAA 3 to 5.4 cm in diameter by internal or external measurement according to ultrasound **AND**
- A systolic BP <150mmHg (unless they require and are already receiving an ACE-inhibitor or amlodipine 10mg daily).

For patients whose systolic BP is >150mmHg at screening, a 6 week course of the diuretic indapamide SR (1.5mg daily) can be given, with re-evaluation of BP in the 6th week. If this treatment is not appropriate then 5mgs of amlodipine can be prescribed if not already taking this drug. If the SBP falls to <150mmHg then subjects will then be eligible for randomisation into the study. If the SBP does not fall <150mmHg, then those subjects that were given indapamide for 6 weeks may then be prescribed 5mgs of amlodipine if not already taking this drug. This would be followed by another 6 week re-evaluation (ie. 12 weeks after screening).

(ii) Exclusion criteria

- Patients who are already required to take either an ACE-inhibitor or a calcium channel blocker or Angiotensin II blocker (ARB) who cannot be converted to diuretic therapy and/or a 5mg dose of amlodipine for control (ie SBP < 150mmHg) of their BP.
- Those with known renal artery stenosis (>50%), or with a serum creatinine of >180µmol/L
- Those unable to give informed consent
- Those too frail to travel for 3-monthly surveillance will be excluded.
- Any clinically significant medical condition which, in the opinion of the investigator, may interfere with the study results and or reduce life expectancy to < 2 years;
- Participation in another trial of an investigational product or device within the previous 30 days;
- Known allergy or sensitivity to perindopril or amlodipine
- Unable or unwilling to comply with the requirements of the study, in the opinion of the investigator.

IV B Procedures and measurements

(i) Recruitment and Screening

The databases at the study sites will be used to identify patients and subsequently inform potential participants about the trial.

At the screening visit participants will first have informed consent taken by the local site principal investigator or delegate. Each subject will be informed of the study's objectives and requirements during the screening visit before any procedures are performed. The investigator or his/her designee will explain the study fully to the subject using the Subject Information Sheet/Informed Consent Form document. If the subject is willing to participate in the study, written informed consent will be requested after sufficient time to consider participation and the opportunity to ask further questions has been given. The Informed Consent Form will be signed and personally dated by both the subject and the investigator or a person delegated to do so by the investigator. The subject will be provided with a copy of the signed Subject Information Sheet/Informed Consent Form document. The original Informed Consent Form will be retained with the source documents.

The initial investigation will be the measurement of BP, to determine eligibility for the trial. If suitable, patients will then undergo the full screening visit.

For most recruiting sites in London, all trial visits subsequent to screening will take place at St Mary's Hospital, London. All other sites will be stand-alone sites that conduct all the trial visits.

(ii) AAA measurement

Trial staff will be trained in ultrasonography by an experienced Vascular Scientist, Corinna Gomm (CG), with training updates and assessments at 6-monthly intervals. The reproducibility of measurements will be enhanced by having a dedicated trial co-ordinator at the scanning sites measuring diameters with a single ultrasound scanner, avoiding inter-observer variation. Images will be stored and a random sample checked by SD at monthly intervals. The workload proposed is feasible (from comparison with co-ordinator workload of up to 350 patients in UK Small Aneurysm Trial and Study (5).

For patients that are scanned as part of this trial by staff that are not qualified vascular scientists or ultrasonographers (ie trained specifically to perform ultrasounds in this trial) the standard duplex ultrasound examination will also take place by a trained vascular scientist at intervals prescribed by the vascular surgeon in charge of the patient. This will ensure continuity and safety of care as well as enable a robust quality control mechanism.

The trials that established that surveillance was a safe, cost-effective policy for small AAAs measured maximum anterior-posterior external aortic diameters. Careful staff training resulted in these measurements having a reproducibility of ±2mm (25). In contrast, the MASS trial of aneurysm screening measured maximum internal aortic diameter (which is 3-6mm less than corresponding external diameter) (26). Following on from this, the National Aneurysm Screening programme proposes to use internal aneurysm diameter, although the reproducibility of this measurement is not reported.

Aneurysm growth rates measured using internal diameters have greater “noise” or scatter than growth rates measured using external diameters (Thompson SG personal communication, research in progress on NIHR HTA 08/30/02). This is consistent with vascular scientist opinion that, particularly in the presence of intra-luminal thrombus, it can be difficult to measure internal diameters accurately. Therefore, we shall record both maximum internal and external diameters on all patients, to enable a reliable comparison and to inform future practice.

(iii) Blood pressure

At the screening visit only peripheral (brachial) BP will be taken.
For visits from baseline onwards, both peripheral and central BP (which has been associated with AAA growth) will be measured using a Pulsecor device (where possible). Central BP is recorded in the same way as peripheral BP but at the same time incorporates an estimate of central aortic BP. The estimates of central aortic BP generated via the Pulsecor will then be compared with AAA growth to evaluate a possible causative association.

At each visit, three BP recordings will be measured in the sitting position using a validated semi-automated device after at least 10 minutes rest. The mean of the second and third readings will be used in analyses. Smoking will not be allowed in the 30 minutes before BP measurement.

The full blood pressure protocol can be found in the Study Procedures Manual.

(iv) Clinical laboratory samples

Blood tests for concentrations of creatinine and electrolytes will be collected at screening, 3, 12 and 24 months (best practice for management of hypertension with ACE-inhibitors)

(v) Biomarker studies

Blood and urine for biomarker studies will be collected at 0 (baseline) and 12 months for patients and sites that agree to participate in this sub-study. The biomarkers to be investigated are NTPro-BNP, thioredoxin and circulating MicroRNAs. Metabolic phenotyping of the samples will also be undertaken using metabonomics.

All biomarker samples will be anonymised at collection and initially processed, aliquoted and stored at The Department of Biosurgery and Surgical Technology, St Mary's Hospital. Metabonomics and analysis of NTPro-BNP and thioredoxin will also take place at this laboratory.

Aliquots for analysis of circulating microRNAs will be transported to and undertaken at The James Black Centre, King's College London.

All samples will be destroyed after the analyses described above.

The full sampling protocol can be found in the Study Procedures Manual.

(vi) Visit Schedule

Stage:	**Identification of suitable patients:**	**Screening & Consent:**	**Randomisation:**	**Treatment:**							
Visit [(1)]	**Suitable patients identified and contacted**	**-1** AAA 3.0-5.4cm? SBP<150mmHg?	**1 (Baseline)**	**2**$^{+}$	**3***	**4***	**5**$^{+}$	**6**$^{\diamond}$	**7**$^{+}$	**8**$^{\diamond}$	**9**$^{+}$
Months [(1)]		-3 to 0	0	3^{+}	6*	9*	12^{+}	15$^{\diamond}$	18^{+}	21$^{\diamond}$	24^{+}
Inclusion & exclusion criteria		**X**	**check**								
Informed consent		**X**	**check**								
Demography		**X**									
Past medical history[(2)]		**X**									
Current medical therapies		**X**	**check**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Ultrasound of AAA	AAA 3.0-5.4cm	**review**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood pressure[(3)]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pill count				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood for creatinine and electrolytes [(4)]		**X**	**review**	**X**			**X**				**X**
Blood and urine for biomarker studies [(5)]			**X**				**X**				
EuroQoL, health resource questionnaire							**X**				**X**

(1)	From baseline onwards visits should occur 3 months +/- 7 days where possible
(2)	Including smoking/alcohol history and height and weight
(3)	Both peripheral and central blood pressure where possible
(4)	Bloods at screening do not need to be taken if creatinine and electrolytes have been performed within the last 6 weeks.
(5)	For sites that agree to participate in the biomarker study
(6)	(+) These visits (month 3, 12, 18 and 24) must be undertaken for those that opt for 6 –monthly visits.
(7)	(*) For those that opt for 6 monthly visits either the 6 month or 9 month must be undertaken
(8)	◇ The 15month and 21 month visits may be omitted if the patient is having 6-monthly visits

(vii) Blinding and Randomisation

Treatment will be single-blind, that is, the subjects will not know which treatment is being taken although the tablets will not be identical. The investigator and pharmacist will retain code lists containing the treatment sequence for each subject

(viii) Study drug administration

Either a three or six month supply of study drug will be dispensed at each visit (depending on whether the patient is undergoing 3-monthly or 6-monthly visits). One tablet should be taken at the same time each morning.

For the initial two weeks following randomisation, patients will be asked to take half doses of the IMP dispensed (ie. 5mg of perindopril, 2.5mg amlopidine and half of the placebo tablet). All patients will be provided with pill cutters at their randomisation visit for this purpose. After two weeks they will instructed to uptitrate to the full dose. This is in line with standard clinical practice for perindopril.

(vi) Treatment and Follow-up

Study drugs will be administered following the randomisation visit at visit 1 and then every 3 or 6 months as appropriate to the patients next visit

IV C End point management

Outcome measures

<u>The primary outcome measure</u> will be aneurysm growth rate, estimated using multilevel modelling. Patients will have their maximum anterior-posterior aneurysm diameter measured by ultrasonography at 3 or 6 monthly intervals, using a dedicated trial co-ordinator.

<u>Secondary outcome measures</u> will include:

The three interventions are ACE-inhibition with perindopril versus equivalent BP reduction with amlodipine (a calcium channel blocker) versus placebo. By comparing the effects in the perindopril and amlodipine arms, this design will permit an evaluation of any BP independent effects of perindopril.

Modelling of time taken for the aneurysm to reach the threshold for intervention (5.5 cm) and formal comparison of the reproducibility of internal and external aneurysm diameters.

Quality of life (Euroquol 5D) and a health resource questionnaires will be administered after 12 and 24 months of follow up.

Intolerance of ACE-inhibitors, drug compliance and BP reduction.

Aneurysm rupture is likely to be too infrequent an event to justify its inclusion as an endpoint in a study of small aneurysms but this information will be collected.

If during the trial an individual patient's aneurysm should reach 5.5 cms in diameter, this patient will be referred back to the vascular surgeons in the normal surveillance programme. This assessment should take place within 2 weeks.

V A ADVERSE EVENT DESCRIPTION:

The following adverse events will be collected.

- A single diagnosis or symptom which leads to discontinuation of the trial drug.
- Duration and severity
- The causal relationship between the IMP and the AE will be indicated:
  Possible, probable or definite

AEs will be followed up according to local practice until the event has stabilised or resolved.

V B Serious Adverse Events (SAE)

An SAE is defined as any untoward medical occurrence or effect that, at any dose:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Any planned/elective hospitalisations that are scheduled prior to signing informed consent but take place during the patients participation in the study do not require reporting as SAE's.

It should be emphasised that, regardless of the above criteria, any additional adverse experience, which the investigator considers serious, should be reported immediately.

Rapid reporting of all SAEs, occurring during the study or within 15 days following the completion of the study by the subject, must be performed as detailed in the Instructions for Rapid Notification of SAEs. However, if the investigator becomes aware of safety information that appears to be drug related, involving

a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

(i) Suspected Serious Adverse Reaction (SSAR)

Any adverse reaction that is classed as serious and which is consistent with the information about the IMP listed in the Summary of Product Characteristics (SPC)

(ii) Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classed as serious and is suspected to be caused by the IMP that is NOT consistent with the information about the IMP in either the SPC or IB, ie, it is suspected and unexpected.

The trial protocol should include a list of known side-effects for each drug in the study. This should be checked with each serious adverse event that occurs in terms of expectedness. If the event is not listed as expected, or has occurred in a more serious form than anticipated, this should be considered a SUSAR.

If the AE is serious and unexpected, the possible, probable and definitely related should be notified to the appropriate regulatory authority as required, the relevant IEC/IRB and the Sponsor as SUSARS.

(iii) Abnormal Laboratory Test Results

Within the study blood estimations of electrolytes and creatinine will be performed at baseline, three months and one and two year visits.
All clinically important abnormal laboratory test results possibly relating to trial medication occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made. The patients GP will be informed and decide if further referral is appropriate.

VI EARLY DISCONTINUATION OF THE STUDY OR INDIVIDUAL SUBJECTS

VI A Early Discontinuation of the Study

Data Monitoring & Ethical Committee

A Data Monitoring & Ethical Committee will be set up to monitor the safety of the pilot trial. Professor Simon Thompson will chair this committee

He will be involved in setting up the committee charter and selecting other expert members of the Board. The planned frequency of any interim analyses will be stated in the Committee Charter as deemed appropriate.

If, in the opinion of the investigator or the Data Monitoring & Ethical Committee the clinical observations in the study suggest that it might not be justifiable to continue, the study may be terminated following consultation with the Sponsor. Alternatively, the Sponsor may give written notification to the investigator, regulatory authorities and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) of the early discontinuation of the study, including reasons.

In case of early discontinuation of the study, the next Follow-up Visit assessment should be performed for each subject, as far as possible. The patient will then be returned to the national screening programme.

VI B Early Discontinuation of Individual Subjects

The reason for a patient discontinuing study medication will be recorded in the case record form. A discontinuation occurs when an enrolled patient permanently ceases taking the study medication, regardless of the circumstances, prior to completion of the protocol. A discontinuation must be reported immediately to the co-ordinating centre and to the Sponsor. It may not be necessary for a patient to stop treatment after an endpoint. The investigator will record the reason for study drug discontinuation, provide or arrange for appropriate follow-up for such patients, and document the course of the patient's condition. *The patients should, if at all possible, be followed to the end of the study despite discontinuation of the study drug* as the intention-to-treat analysis includes all patients.

Typically, subjects may discontinue study medication for the following reasons:

a. At the request of the subject.

b. If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develops after entering the study.

For any subject who discontinues therapy before the study is completed, the investigator will:

a. Complete the case record form including any summary sheet, indicating the date of and explanation for the early discontinuation of medication. If possible, provide an overall evaluation of safety of the assigned treatment.

b. If necessary, arrange for alternative medical care of the discontinued subject

c. Follow the patient in the usual way to the end of the study despite discontinuation of the study medication**.**

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. In case of early discontinuation of a subject, the Follow-up assessments should be performed, as far as possible.

VII STATISTICAL ANALYSES

VII A Randomisation

Arrangements for randomisation

Data for this trial will be collected via the electronic data capture system called InForm. This system will be managed on a day to day basis by the Imperial College IT department.

This system will also be used to administer the randomisation of the patients. This will entail the trial statistician providing the Inform administrative staff with the randomisation codes so they can be incorporated in to the system.

Randomisation will be performed using a 1:1:1 ratio between the 3 randomised groups and stratified by centre and by baseline size of aneurysm stratified into two size ranges; 3.0 to 4.5cm and 4.51 to 5.40cm. This will be necessary as growth rates have been shown to increase with aneurysm diameter. The randomisation code will be generated using randomly permuted blocks of varying sizes using Stata

computer software (Stata Corporation, Texas, USA).
Once the subject has given written informed consent, he/she will be randomised and allocated a unique study number for use in all future data collection for that patient.

Treatment will be blind, that is, neither the subject nor study site staff will know which treatment is being taken. The investigator and pharmacist will retain the randomisation codes for each subject (Section 9.5) none of the study drugs will be identical in appearance to each other although the packaging (Section 9.1) will not enable them to be told apart as it will be identical.

VII B Sample Size

Statistical Analyses

Assessment of AAA growth rates

Random effects multilevel modelling methods will be used to assess AAA diameter over time. A random slopes and intercepts model will be fitted and non-linear effects will be investigated to create the most parsimonious model. Comparison of treatment groups will be by 'intention to treat' however if compliance with randomised group is poor, a per protocol analysis will be considered and defined according to an a-priori set of criteria.

Primary outcome

The difference in AAA growth rates between placebo and ACE-inhibitor treatment groups will be the primary outcome. The multilevel model will be used to present this difference as a crude estimate as well as one adjusted for an a-priori list of potential confounding variables between groups.

Secondary outcomes

Influence of blood pressure reduction

In order to investigate how much difference in growth rate between placebo and ACE-inhibitor is attributable to BP reduction, a third randomised group will treat patients with amlodipine (a calcium channel blocker). A test of interaction will be used to investigate whether the treatment effect of amlodipine relative to placebo is significantly different from the treatment effect of perindopril (ACE-inhibitor) relative to placebo. Given that tests of interaction tend to have limited power, additional analyses may be considered that adjust the random effects growth rate models for blood pressure at the time of aneurysm diameter measurement.

Time to AAA rupture or elective AAA repair

Small AAA (<5.5cm) rupture infrequently (<1% per annum) (6, 27)and insufficient events would be available to test this outcome alone. However, a number of patients will proceed to elective AAA repair during their follow-up period, usually once the AAA increases to beyond 5.5cm, becomes symptomatic or starts to grow particularly rapidly (>1cm/year). Using the outcome of the proportion of patients either rupturing or undergoing elective AAA repair, the target recruitment of 75 patients in each of the ACE-inhibitor and placebo groups would provide 90% power at the 5% significance level to detect a difference of 10% and 33% respectively. Survival analysis techniques such as Cox proportional hazards models will be used to assess this outcome. Comparison of treatment groups will be by 'intention to treat'.

Subgroup Analyses

As this is a pilot trial of 225 patients, the number of patients in each group is unlikely to be large enough for meaningful subgroup analyses. No subgroup analyses are therefore planned.

VII C Data Analysis

A statistical analysis plan (SAP) will be written and finalised prior to any lock of the study database. The SAP will give a detailed description of the summaries and analyses that will be performed.

(i) Missing, Unused and Spurious Data

A strategy for handling missing data will be developed for missing data. The strategy will depend on the extent and type of missing data (missing completely at random, missing at random, not missing at random). For missing baseline data, the most likely strategy will be multiple imputation by chained equations (MICE). If significant follow-up data are missing for aneurysm diameter and BP, more complex methods may be employed if it is felt to be necessary. The importance of complete data for the aneurysm diameter, BP and proposed confounder variables for the adjusted analyses will be prioritised as part of the data collection.

(ii) Deviations from the Statistical Plan

The statistical analysis plan will be written and finalised prior to any lock of the study database. It will give a detailed description of the summaries and analyses that will be performed and clearly describe when and by whom these analyses will be performed. Any deviation(s) from the original SAP will be described and justified in the clinical study report.

(iii) Baseline Characteristics

Baseline characteristics will be compared between the randomised groups. The SAP will have already pre-defined a list of variables for adjustment in the analyses, however, if chance differences in other baseline covariates are apparent, sensitivity analyses will be performed to see whether adjustment for these alters the findings appreciably.

(iv) Safety Analysis

Given that this is a pilot trial of just 225 patients, it is anticipated that very few serious adverse events will have occurred by the end of the study. Therefore, crude percentages of patients will be presented to inform the design of a larger trial but no statistical comparison will be made between randomised groups.

(v) Interim analysis for early stopping

The frequency and timing of any interim analysis will be determined by the Data Monitoring and Ethical Committee (DMC) and analyses will be performed by an independent statistician. The interim analyses results will be reported directly to the DMC.

VII D Data Management

The Inform data management system will be used.

VIII TREATMENT

VIII A Investigational Medicinal Product Details

The perindopril, amlodipine and placebo will be produced in accordance with Good Manufacturing Practice, and packaged and labelled by The Royal Free Hospital Pharmacy Manufacturing Unit, Pond Street London NW3.

The amlodipine, perindopril and placebo will be packaged by the Royal Free and the packaging will appear identical.

The indapamide 1.5mg SR or amlodipine 5mg for use in the treatment of blood pressure of those with a SBP>150mmHg following the initial screening visit will be supplied by the site pharmacy or patients GP in blister packs (not blinded).
Losaratan 100mg for use in patients who develop a cough within the trial will be supplied by the site pharmacy or from the patients GP in blister packs (not blinded).

VIII B Labelling, Storage and Dispensing

For patient having 3-monthly visits, 100 tablets sufficient for 14 weeks treatment will be dispensed at each study visit. For patients that opt. for 6 monthly visits – 200 tablets may be dispensed as appropriate to the date of their next visit.
Labelling will be in accordance with Good Manufacturing Practice (GMP). Each bottle will be labelled, as a minimum, with the study identification and randomisation number.
IMP must be stored at not above 25°C in a secure area, free of environmental extremes. Storage and dispensing of IMP will be the responsibility of the investigator or designee or pharmacist. This person will monitor the temperature of the storage area where the study medication is kept.

VIII C Dosage, Duration and Compliance

Following randomisation, half a tablet should be taken at the same time each day after breakfast for the first two weeks, and then one tablet each day thereafter.

In the case of adverse events, the patient should be assessed by the PI or delegate to decide if any action needs to be taken in regards to the dose of IMP. The PI may suggest that the patient down-titrates to half a tablet temporarily or for the remainder of the trial. The PI may also decide to temporarily stop the IMP if necessary. All dose changes (including dose reductions or temporary stopping of the drug) should be recorded on the relevant forms.

VIII D Accountability

On receiving a shipment of IMP at the site, the investigator or designee will conduct an inventory check and complete a supplies receipt document, a copy of which will be retained at the site; the original must be returned to the Sponsor or designee.

During the study, the investigator or designee will record the quantities of IMP dispensed to and returned from the subject in a dispensing log. Drug accountability will be monitored.

The investigator or designee will arrange for all unused IMP to be destroyed according to local procedures after accountability and compliance assessments have been completed. Confirmation of destruction will be provided to the Sponsor.

VIII E Code-breaking

The electronic randomisation codes will be held by the pharmacy in each of the centres. In the event of a request for un-blinding to take place this should be referred to the site Principal Investigator and the study

coordinator. If this request occurs out of hours then un-blinding may take place at the discretion of the on-call pharmacist.

IX REGULATORY, ETHICAL AND LEGAL ISSUES

IX A Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the [2008] revision of the 1964 Declaration of Helsinki.

IX B Good Clinical Practice

The study will be conducted according to the protocol and to Standard Operating Procedures (SOPs) that meet the current regulatory requirements and guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines) in clinical studies.

IX C Independent Ethics Committee/

Ethical and Regulatory Arrangements

The study protocol and related documents will be submitted for ethical and R&D approvals, through IRAS for multisite approvals. The submission will be supported by appropriate patient information sheets and consent forms and other materials relating to participation. Site-specific information will be submitted by each participating NHS Trust. The trial will be registered with clinicaltrials.gov and a NCT number obtained. Authorisation will also be sought from the national competent authority – the Medicines and Healthcare products Regulatory Agency. The study shall not commence before all necessary approvals have been received.

(i) Initial Approval

Approval will be sought from an Independent Ethics Committee.

(ii) Approval of Amendments

All protocol amendments will be submitted to this ethics committee for approval. Likewise to the regulatory authorities

(iii) Reporting of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs; also known as serious adverse drug reactions) occurring during the study at any investigational site will also be reported to the IEC and the MHRA within the required timelines. The actual reporting of the events will be performed as instructed by the Sponsor.

(iv) Annual Safety Reports and End of Trial Notification

These will be submitted to ethics and the MHRA

IX D Regulatory Authority Approval

The study will be performed in compliance with regulatory requirements. Clinical trial authorisation will be obtained from the MHRA. This trial will be sponsored by Imperial College London and will be conducted within the proposed centres within London. Coordination of the study will be the responsibility of ICTU. ICTU provides core staff within an infrastructure supporting the management, monitoring and reporting of clinical trials involving investigational medicinal products. ICTU has systems in place to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Adverse events will all be notified to the Data Safety and Monitoring Committee who will respond accordingly and communicate any relevant action steps to the Trial Management Committee via the Trial Steering Committee.

This study will not open to recruitment until appropriate approvals and authorisations have been obtained from an independent ethical committee and the Medicines & Healthcare Products Regulatory Agency. Recruitment will not commence at an individual participating site until local NHS Management approval has been obtained and, all local documentation is in place and all requirements have been fulfilled according to ICTU Standard Operating Procedures (SOPs).

IX E Insurance

The Sponsor has civil liability insurance with Novae Insurance Company Ltd which covers this study in the UK

IX F Pre-study Documentation Requirements

The following documents will be required before the IMP can be shipped to the investigational site:

- Signed and dated Secrecy Agreement
- Signed and dated protocol and any amendment
- Copy of the IEC/IRB-approved Subject Information Sheet and Consent Form and other written information given to subjects
- Copy of the written IEC/IRB approval of the protocol (and any amendments), Subject Information Sheet and Consent Form, other written information given to subjects, advertisements, and any subject compensation
- Curriculum vitae of the Principal Investigator (signed and dated)
- List of IEC/IRB members and a statement of compliance with ICH GCP, or copy of IEC/IRB constitution.
- Documented Regulatory Authority approval/notification
- Signed and dated Clinical Trial Agreement
- Insurance certificate/letter of indemnity
- Emergency code break procedures; Instructions for handling IMP and Certificates of Analysis
- Sample of the final IMP label
- Receipt of the Summary of Product Characteristics/Product Information Leaflet

IX G Informed Consent

It is the investigator's responsibility to obtain written informed consent from the subject/ after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are commenced. The subject representative should be given a copy of the Subject Information Sheet and Informed Consent in their native language. The original copy of the signed and dated informed consent must be retained in the institution's records, and is subject to inspection by representatives of the Sponsor, or representatives from Regulatory Authorities.

IX H Contact with General Practitioner

It will be the investigator's responsibility to inform the subject's General Practitioner/Primary Care Physician by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter will be filed in the Investigator Site File.

IX J Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.
The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and IECs/IRBs.

IX K Data Protection

All personnel involved in the study will observe or work within the confines of the local data protection regulations.

IX L End of Trial

The end of the trial is defined as the date of the last patient attending the last (final) study visit.

IX M Study Documentation and Data Storage

Retention of Documents
This trial will be coordinated by the Imperial Clinical Trials Unit (ICTU) who has in place well established protocols for the protection of data and facilities for retention of documents. Data will be stored for a minimum of 10 years (or according to changes in regulatory requirements) following completion of this trial. Data generated by this work will be processed in accordance with the Data Protection Act 1998. ICTU will adhere to the Imperial College Code of Practice, drawn up in association with the College's Data Protection Policy, relating to the collection, holding and disclosure of data relating to individuals. The Principal and Co-applicants will act as custodians of the data, and be responsible for its security. The PI will ensure the continued storage of the documents, even if they leave the clinic/practice or retire before the end of the required storage period. Delegation will be documented in writing.
The PI at each investigational site is responsible for the archiving of all the essential trial documents, including the Investigator Site File, in accordance with regulatory requirements.

The investigator must retain a comprehensive and centralised filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of Regulatory Authorities.

The investigator must retain essential documents until notified by the Sponsor, and at least for ten years after study completion, as per Directive 2005/28/EC Article 17. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be give to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

X ADMINISTRATIVE MATTERS

Trial management and Research Governance

The trial will be coordinated by the Imperial Clinical Trials Unit, which holds provisional registration as a UKCRC Registered Trials Unit. The Director of the National Aneurysm Screening programme, Mr Jonothon Earnshaw will chair the Trial Steering Committee and this committee will include a patient representative. Professor Simon Thompson has agreed to chair a Data Monitoring & Ethical Committee. The Trial Management Committee if possible including a patient representative will be chaired by Professor Neil Poulter.

The trial will be registered on the clinical trials.gov website.

X A Electronic Recording of data

(Electronic CRF): The principal means of data collection from patient visits will be Electronic Data Capture (EDC) via the internet. Data is entered into the EDC system via site personnel. All data recorded in the CRF will be signed by the Investigator or his/her appropriate designee. All changes made following the electronic signing will have an electronic audit trail with a signature and date. Specific instructions and further details will be outlined in SOPs and/or manuals.

All laboratory reports (if applicable) will be reviewed, signed and dated by a clinician.

X B Structure:

The co-ordinating centre will be at the Imperial Clinical Trials Unit.

Committees
The following study committees will be established:

- **Trial Management Committee**
  Responsible for the day to day running of the study
  To include chief investigator, patient representative and project manager

- **Trial Steering Committee**
  To provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice. Chaired by Professor Jonothan Earnshaw (Hon Sec VSGBI)
  With Professor Cliff Shearman
  Include the chief investigator and the patient representative

- **Data Monitoring and Ethical Committee**
  Chaired By Professor Simon Thompson
  Dr Tuen Wilmink
  Professor Gareth Beevers (TBC)

- **Data Verification (QC)Committee**
  To verify data collected from ultrasound examinations.
  Ms Corinna Gomm to co-ordinate

X C Monitoring

The study will be monitored by ICTU trained monitors following a risk assessment, in accordance with GCP

X D Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection. Additionally, an ultrasound quality assurance event will be organised to evaluate the standard of measurement that is being achieved by the collaborating research teams for the study. The event will provide an opportunity for all scanning staff to measure and record AAA measurements of volunteer AAA trial patients. The aim is to assess the inter-observer and intra-observer variability of the measurements taken by the scanning staff. Analysis of the results obtained from this event will be carried out by statisticians on the study team at the coordinating centre.

X E Disclosure of data and publication

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

Service users

Several patients with small AAA have been consulted to seek their opinions about the design and running of the proposed trial. All these patients reported that they would feel reassured by the increased surveillance of their AAAs. In addition, a close relative of one patient approached emphasised the painful and stressful nature of the surgery his relative had undergone and how he wished there had been an alternative to that surgery. Therefore, anything which could be done to slow the growth of the AAA, to prevent or delay the need for distressing major surgery was seen as being positive. One of these patients is willing to act as a consultant to the trial management team.

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SIGNATURE PAGE 1 Chief Investigator

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Signed: _____

Professor Neil Poulter
Chief Investigator

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Signed: _____

Sponsor's Representative

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Signed: _____

Name :

Date: _____

SIGNATURE PAGE 4 (INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____