IMPERIAL

CLINICAL STUDY PROTOCOL

(ICTU ADOPTED)

Full Study Title: Women's Aneurysm Research: Repair Immediately or Routine Surveillance, Trial and Registry

Short Study title / Acronym: WARRIORS

Sponsor: Imperial College London

Version no: 2.0

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This protocol has regard for the HRA guidance.

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This protocol describes the WARRIORS trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AAA	Abdominal Aortic Aneurysm
AE	Adverse Event
BMT	Best Medical Therapy
BP	Blood Pressure
CI	Chief Investigator
CSH	Cause Specific Hazard
CT	Computerised Tomography
CTA	Computerised Tomography Angiography
DMEC	Data Monitoring and Ethical Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	Euroquol descriptive and visual analogue scale for quality of life
EVAR	EndoVascular Aneurysm Repair
f-EVAR	Fenestrated EndoVascular Aneurysm Repair
HRA	Health Research Authority
HADS	Hospital Anxiety and Depression Scale
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intention to Treat
MACE	Major Adverse Cardiovascular Events
QA	Quality Assurance
QALY	Quality-Adjusted-Life-Year
QC	Quality Control
QoL	Quality of Life
QRI	Quintet Recruitment Intervention
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL SUMMARY

TITLE

Women's Aneurysm Research: Repair Immediately or Routine Surveillance, Trial and Registry. A randomised trial to assess the clinical effectiveness of early endovascular aneurysm repair in women with small abdominal aortic aneurysm) - WARRIORS trial.

OBJECTIVES

Primary aim: For women with small abdominal aortic aneurysm (AAA, 4.0-5.4 cm diameter), to assess whether early endovascular aneurysm repair (EVAR) compared to routine surveillance decreases the composite outcome of AAA rupture and aneurysm-related mortality over five years.

Secondary aim: For women with small abdominal aortic aneurysm (AAA, 4.0-5.4 cm diameter), to assess whether early endovascular aneurysm repair (EVAR) compared to routine surveillance increases quality-adjusted-life-years (QALYs) over five years.

Other aims: to compare operative mortality, anxiety, major cardiovascular events (MACE), all-cause mortality, costs and cost-effectiveness between the two randomised groups. Also, in the surveillance group to assess the rate of losing eligibility for EVAR as the AAA expands.

DESIGN

WARRIORS is an international multicentre, open label, superiority RCT, randomly allocating consenting women with small AAA, morphologically suitable for EVAR in a 1:1 ratio to either early EVAR or routine ultrasonographic surveillance. This will be an international trial anchored in the UK, where there will be 15-18 recruiting sites, each aiming to randomise 10 patients. The named UK collaborators are Olivia McBride (Dundee), Rachel Bell (Newcastle), Matthew Bown and Rachel Evley (Leicester), Ian Loftus and Manuel Gomes from London (St George's Hospital and University College London respectively). There will be a further ~100 recruiting sites from across the world, including North America, Europe and Australasia. In total the trial plans to randomise 1112 women in 1:1 ratio of either early EVAR or routine surveillance with delayed repair for either AAA rupture or reaching the threshold diameter of >5.4 cm. There will be a Vanguard phase, enrolling 250 patients internationally, of 250 patients to confirm both the feasibility of recruitment, and that the safety of the policy of early EVAR is within the range reported by observational studies from the USA. The primary composite outcome of aneurysm-related mortality and aneurysm rupture will be assessed at 5 years after randomisation.

SAMPLE SIZE

1112 women with small AAA, identified from trial vascular centres in 8 or more countries.

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

- female sex
- age ≥50 years
- infra-renal abdominal aortic aneurysm with a maximum infrarenal aortic anterior-posterior diameter 4.0-5.4 cm, aneurysm, measured on ultrasonography or the centreline orthogonal diameter on Computed Tomography (CT) scan when this is the discovery imaging mode,
- Local assessment that arterial morphology is suitable for EVAR within manufacturer's IFU for any licensed infrarenal endograft, including those with concomitant common iliac aneurysm(s), provided the device is landed in the iliac arteries, without coverage of patent internal iliac arteries.
- Rockwood frailty score <7.

Exclusion criteria:

- Male sex
- aneurysm of the infrarenal aorta of <4.0 or >5.4cm
- infrarenal aneurysm not meeting IFU for any specific licensed endograft for standard EVAR
- inability to give informed consent
- previous abdominal aortic surgery
- age <50 years
- concomitant thoracic aortic aneurysm of >4.0cm diameter
- excessive frailty (Rockwood score ≥7)
- life expectancy <2 years in the opinion of the investigator
- severe contrast allergy not amenable to pretreatment with steroids/antihistamines (e.g. anaphylaxis)
- those considered unlikely to comply with follow-up
- concomitant common iliac artery aneurysm unless: a) the arterial morphology is within the IFU for standard infrarenal EVAR; or b) the arterial morphology is suitable for a licensed iliac branch device; or c) the internal iliac artery is occluded and the stent limb can be landed in the external iliac artery without embolisation of the internal iliac artery.

Excluded women with AAAs ≥4.0 cm diameter will still be eligible for inclusion in a parallel registry.

There will be no patient excluded as a result of geographical location, disability, gender, marriage and civil partnership status, ethnicity, religion or belief, sexual orientation, socioeconomic status or access to health or social care.

INTERVENTION

Early EVAR within a target of 8 weeks of randomisation, with routine follow up.

COMPARATOR: ultrasonographic surveillance with surgery for aneurysm dilation >5.4 cm or AAA rupture.

MAIN STUDY PROCEDURES

CTA to determine eligibility for EVAR (within Manufacturers' Instructions for Use, IFU), if not existing in the previous 6 months. This CT scan also should report the centreline orthogonal diameter, which must be between 4.0 and 5.4 cm to be eligible for randomisation.

Randomisation will be stratified for country, age (≤75 and >75 years) and aneurysm diameter (4.0-4.9 and 5.0-5.4 cm).

Women in the early EVAR group will undergo early EVAR, target within 8 weeks of randomisation, and post-operative clinical and imaging assessment at 4-12 weeks after repair, according to local protocols.

Advice on BMT and recommendations regarding the indications for late AAA repair in both groups will be provided to general/family practitioners caring for the randomised patients.

All women will undergo clinical assessment, at least annually for at least 5 years, with imaging of their aorta by ultrasound, Duplex. CT or other modality as in routine use at the local site. All women will complete a health diary. Virtual or telephone clinical follow up methods are acceptable, where this reduces the burden on local sites.

All women will be asked to complete quality of life (EQ-5D-5L) and anxiety (HADS) questionnaires at their 1,3- and 5-year follow-up, which should be completed before any imaging studies at these time points.

Each patient will be followed up for a minimum of 5-years.

OUTCOME MEASURES

An independent adjudication committee will be convened to review primary endpoint reports submitted by sites.

PRIMARY ENDPOINT

Composite of AAA rupture and aneurysm-related mortality at 5 years.

SECONDARY ENDPOINT

QALYs at 5 years (from quality of life and all-cause mortality)

OTHER ENDPOINTS

- Operative mortality
- Anxiety

- Costs
- Cost-effectiveness
- Loss of eligibility for EVAR at the 5.5 cm diameter threshold
- Major adverse cardiovascular events (MACE), comprising myocardial infarction, stroke and lower limb amputation

1. BACKGROUND

1.1 Clinical Setting

Women have smaller arteries and lower AAA population prevalence, but this is disputed and dependant on diagnostic threshold. AAA is ~5 times more common in men if a 3 cm diameter threshold is applied but only ~1.3 times greater when an increase of >1.5 times the normal infrarenal aortic diameter is used [1]. Women were under-represented in the four major RCTs of small asymptomatic AAA repair, comprising on average only 4.3% of participants. These trials have defined the risk-benefit and intervention threshold for AAA in men, but do not represent women. This is highly pertinent, as women have 4 times greater rupture risk of small AAA [2]. Individual patient meta-analysis (15475 people) demonstrated that in women the rupture risk at 4.2cm diameter was the same as at 5.5cm for men [3]. Increased AAA size is also associated with increased operative complexity and peri-operative mortality. Every 1 cm increase in diameter is associated with an 18% increase in adjusted odd of 30-day mortality for open repair [4]. For EVAR, increased size is also significantly associated with a reduction in both 30-day and 5-year survival [5, 6]. Systematic review with meta-analysis demonstrates that women have higher operative mortality and complications rates than men - 30-day mortality following elective open repair is 6% and for EVAR 2.3% (odds ratio versus men 1.49 and 1.86 respectively even after adjustment for co-morbidities) [7, 8]. These disparities are consistent worldwide and have not ameliorated with time. With a 30-day mortality of 6% open repair cannot be considered a safe elective procedure for women. EVAR is the preferred treatment modality among most AAA patients. Eligibility for EVAR by anatomical criteria declines at significantly lower AAA diameter for women compared to men [9]. At the 5.5 cm diameter threshold, women are less likely to be selected for endovascular repair than men (34% vs 54%) and more likely to be selected for conservative management (34% vs 19%) [10]. Overall, women are 25% less likely to receive elective AAA repair, but increasingly likely to present with AAA rupture, which carries >10-fold increased mortality. Therefore, it is possible that the opportunity for effective AAA treatment in women is being missed. While various retrospective analyses have called for sex-specific criteria for AAA repair [11] , without dedicated prospective research, uncertainty regarding the risk-benefit threshold and sex-specific disparity in AAA repair remain.

1.2 Intervention Details

This is early (target within 8 weeks of randomisation) endovascular infrarenal abdominal aortic aneurysm repair (EVAR), using any approved device within the manufacturer's instructions for use. Newly approved devices will be added and any advances in technology tracked.

1.3 Rationale for Study

AAA repair should be offered when the risk of AAA rupture exceeds the risk of surgery. The diameter threshold for AAA repair was set from randomised trials in which women were underrepresented. It is not known whether offering repair at a smaller size is beneficial in women. There are no pilot trials to test this hypothesis. However, observational evidence indicates that women might benefit from operative repair at a smaller size as the rupture rate is higher in women and operative repair is more likely to be safer. At smaller AAA diameters more women are suitable for minimally invasive surgery and all the available evidence indicates that the outcomes of EVAR are better in patients with smaller AAA diameter, as 30-day mortality following EVAR for small AAA in women is lower than the pooled systematic review estimates for larger aneurysms

(0.5-1.5% versus 2.1%). Early repair also is likely to increase eligibility for the low-risk EVAR, since in women eligibility declines by almost half between 4 and 5.5 cm diameter, and with newer meaning that half of larger AAA need the high-risk open repair or f-EVAR or may not be offered any repair at all. Newer endografts with conformable necks have widened further the eligibility of women with small AAA for EVAR to as high as 85%.

Clinician equipoise for randomisation and AAA diameter range for inclusion has been ascertained by questionnaires to vascular surgeons in Germany, the UK, and the USA (84-92% in favour). The proposed trial has been presented at vascular conferences, with widespread acceptance of its need. In the UK 84% of vascular surgeons have equipoise and would be willing to randomise patients (of low and moderate operative risk in the AAA diameter range 4.0 to 6.0 cm). In Germany, 91% of vascular surgeons have equipoise and would support the trial (for all operative risk categories, predominantly in the diameter range 4 to 5.4 cm, although some would randomise to 6 cm): results from the USA were similar. Consultations with other clinicians in Canada, the Netherlands and Nordic countries have agreed that the trial addresses a key question with widespread equipoise and willingness to participate. The trial has received favourable opinion from London and Manitoba-based patient groups. In the UK, 17/18 individual patients would consider/have considered randomisation and in Germany, 7/10 women indicated that they would accept randomisation, as two were anxious about surgery and one wanted earlier repair.

1.4 Risk/Benefit Assessment

There are no evidence-based guidelines for the management of AAA in women, although it is recognised widely that women should be offered AAA repair at smaller diameters than men. Aneurysm repair balances the risk of repair (operative mortality and complications) with the later risk of AAA rupture (which is fatal in >80% cases) without repair: early pain for later gain? Many studies support the tenet that operative mortality and complications are lower for smaller AAAs and at younger ages. In women, early repair boosts their chances of being eligible for the low-risk EVAR procedure, with an estimated 30-day mortality of 1.5%. This early risk is likely to be outweighed by the risks of AAA rupture (1.5 per 100 woman-years) and the eventual risk of surgery in over half of women, more often using the high-risk procedures of open repair or f-EVAR (operative mortality 5-10%) at an older age for a larger AAA. Factored into these scenarios is the anxiety that many women feel about their AAA and how this anxiety may influence their quality of life.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The objective of this trial is to minimise the disparity in outcomes for AAA between men and women by testing the hypothesis that in women will have improved outcomes if treated earlier than at present (for smaller diameter AAA and therefore at younger ages). Specifically, we will test the hypothesis that in women with small AAA, early repair using EVAR will reduce the incidence of AAA rupture and aneurysm-related mortality at 5 years after randomisation.

2.2 Secondary Objectives

Secondary aims are to assess the impact of early AAA repair in women on their quality of life and overall survival (measured as QALYs at 5 years after randomisation).

2.3 Primary Endpoint

The Primary outcome will be the composite of AAA rupture and aneurysm-related mortality at 5 years. Aneurysm-related mortality will include any death within 30 days of AAA repair, death in hospital at beyond 30 days for the index admission for AAA repair and at the same time-points after reinterventions following the index AAA repair, and death from repair or rupture of a supra-renal or iliac aneurysm.

An independent adjudication committee will be convened to review endpoint reports submitted by sites. The committee will be multispecialty and include vascular surgeons, cardiologists, and general/family practitioners. The committee will be blinded to participant allocation. Any reports submitted by sites that could unblind a participant will be redacted prior to submission to the adjudication committee (e.g., radiology report stating trial allocation or treatment).

2.4 Secondary Endpoints

The secondary outcome of QALYs will be based on quality of life collected at baseline, 1, 3 and 5 years using the EQ-5D-5L questionnaire and all-cause mortality over time to 5 years, with death taking a zero rating for QoL

Table 1. Summary of Objectives and Endpoints

Objectives	Endpoints	Timepoint(s) of evaluation of this endpoint
Primary Objective	Composite of AAA rupture and aneurysm-related mortality	Five years
Secondary Objective	Quality adjusted life years (based on quality of life and all-cause mortality)	Five years
Other Objectives	Operative mortality Anxiety Costs Cost-effectiveness Loss of eligibility for EVAR MACE	30 days 0.1,3 and 5 years Five Five years Five years Five years

3. STUDY DESIGN

3.1 Design

WARRIORS is an international, multicentre, open label, superiority RCT, randomly allocating consenting with small AAAs, morphologically eligible for EVAR, in a 1:1 ratio to either early AAA repair by EVAR or to routine ultrasonographic surveillance. It will have a Vanguard phase with adjudicated endpoints. Each participant will be followed up for 5-years.

In the UK, 15-18 sites will be opened at vascular centres, to recruit and provide clinical care for 150 patients (13.5%of total target). The remaining patients will be recruited by participating countries worldwide.

The trial will start with an international Vanguard phase, to optimise and confirm randomisation rates and patient safety (operative mortality rates and ensure inclusivity of underserved groups. In both the UK and other countries, the Vanguard phase is schedule to start in 2025. Women will be recruited over 12 months during which period there will be an ongoing programme of qualitative research to optimise recruitment and ensure representation of minority and underserved groups. The Vanguard trial will run for a further 6 months, to allow completion of interventions and post-operative follow up and analysis of the results. The international Vanguard trial is scheduled to run for one year following the opening of >25% of target sites per participating country to assess and feasibility (recruitment) and safety (operative mortality, aneurysm exclusion and complications). support recruitment rates. The Vanguard phase should be completed within the first 30- months of the trial and include a total of 250 women (including 50 from the UK) and with total accrual of 35 patients/month between months 6-12. The qualitative work to optimise recruitment will use the Quintet Recruitment Intervention (QRI) [12], to identify recruitment obstacles and facilitate improvements to the recruitment process, and the SEAR framework [13], to capture ethnic and diversity characteristics and highlight any discrepancies in the recruitment process, which may negatively impact underserved groups participating (details given below). If only 150-249 have been recruited, improvement measures/additional centres will be introduced to achieve the target accrual of 35/month, with re-evaluation (after a further 6 months). Remedial measures could include visiting and motivating centres, implementation of actions arising from the qualitative work (including improving patient-facing material), running focus groups with those identifying patients including vascular nurses and sonographers, the opening of reserve sites, and an incentive programme (e.g. rewards for recruiting every 50th or 1100th woman). If <150 patients have been randomised and current monthly recruitment is <35/month for months 10-12, the trial should be stopped.

The results of the Vanguard trial should enable the DMEC to set stopping rules for the rest of the trial, based on operative mortality and major complications. In the Vanguard phase, we propose that 30-day mortality for early elective EVAR group should not exceed 3%, but this will need the agreement of the DMEC.

The planned targets for the international Vanguard trial are given below.

Table 2. RAG Criteria for the International Vanguard trial (times from start of BHF funding)

International stop/improve/go milestones	Red	Amber	Green
Sites open by 12 months	6%	16%	28%
Sites open by 18 months	15%	50%	65%
Recruitment by 24 months	80	150	250
Recruitment rate at 24 months/m	10	22	35

Table 3. UK Vanguard Trial in More Detail

Stop/improve/go milestones for UK	Red	Amber	Green
Ethics & database piloted by 6 months after activation of BHF grant			
UK centres signed up to participate at 12 months after activation of BHF grant	<10	10-15	≥16*
Sites open by 12 months after activation of BHF grant	<2	2-4	>5
Sites open by 18 months after activation of BHF grant [6 months after commencement of Vanguard phase]**	≤6	6-11	≥12
Recruitment by 18 months after activation of BHF grant [6 months after commencement of Vanguard phase)	<10 (<20%)	10-19 (20-39%)	≥20 (≥40%)
Recruitment by 24m after start of BHF grant (% total Vanguard target) end of Vanguard phase	≤20 (≤40%)	21-42 (42-84%)	43-50 (≥85%)
Recruitment rate per month at 24m (target 5/m)	≤2	3-4	≥5 (>95%)
Questionnaire data completions	<70%	70%-85%	>85%

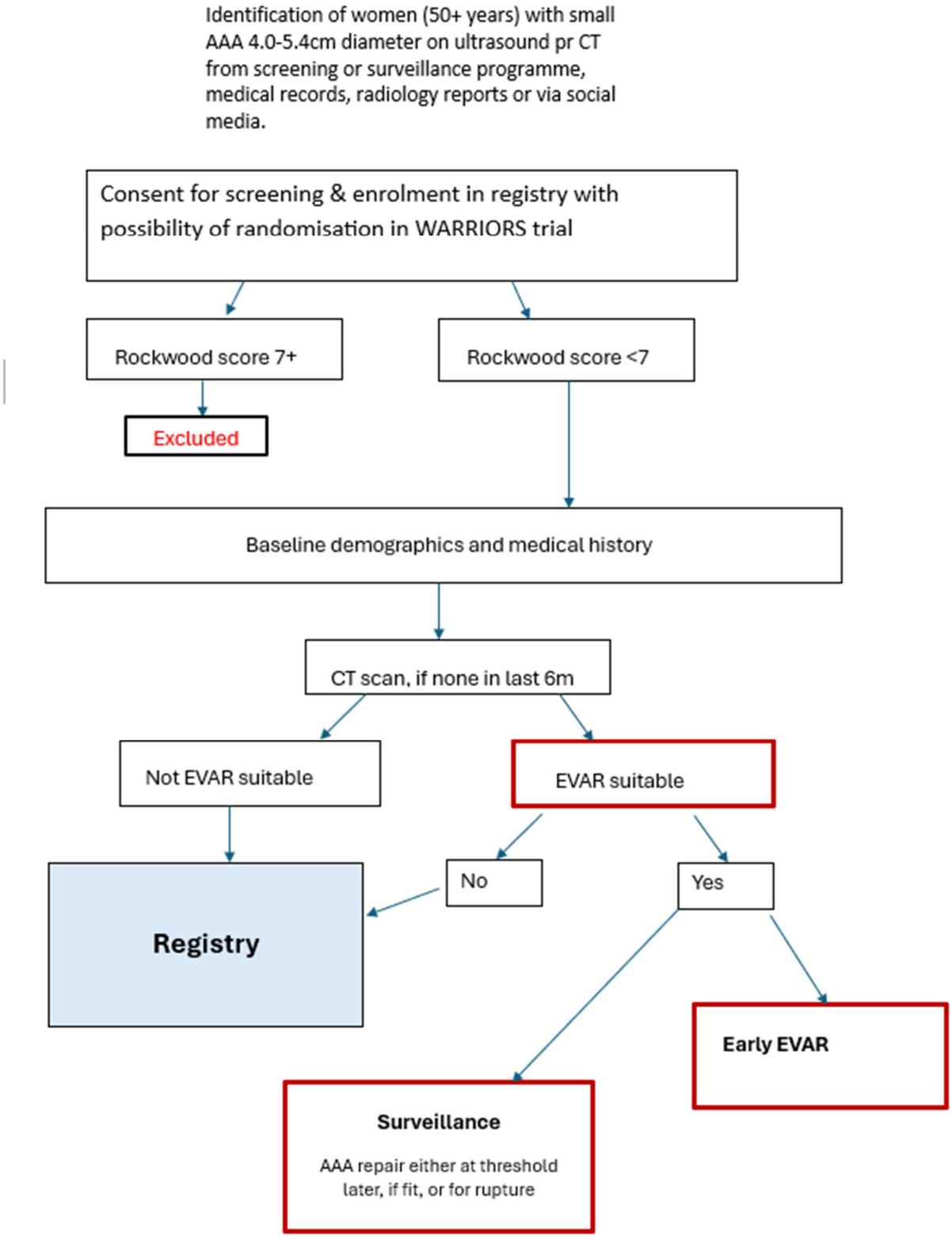
*Overshoot, since some may get delayed

Table 4. Milestones from start to completion of UK Vanguard trial, showing parallel international Vanguard trial (times from start BHF funding)

Milestone	q2 24	q3 24	q4 24	q1 25	q2 25	q3 25	q4 25	q1 26	q2 26	q3 26
Ethics approval										
Funding start										
Database										
Database pilot										
Centres opened				3	6	13	16			
UK Vanguard randomisation								50		
Qualitative work Optimise recruitment										
UK Vanguard data completion										
International Vanguard recruitment										
International data completion										
Vanguard analysis										

The performance and results of the Vanguard trial will be scrutinized by both the Trial Steering Committee and the DMEC.

Figure 1: Study Flow Chart



4. SUB-STUDY - Quintet Recruitment Intervention (QRI)

4.1 Objectives

The aim of the QRI is to work with WARRIORS trial clinical research teams to understand the recruitment process in the early stages, so that any difficulties related to design or conduct can be raised and changes put in place. Specifically:

1 To determine any training that needs to be developed or feedback given to members of the clinical care team approaching and recruiting patients.

2 To determine any modifications in patient-facing materials that would improve the inclusivity of patient recruitment.

4.2 Outcomes

(a) Primary outcome. More than half of eligible women accept randomisation.

(b) Secondary outcome. To increase (by ?10%) the representation of patients of diverse ethnic, socioeconomic and educational backgrounds in the trial.

4.3 Design

The Quintet Recruitment Intervention (QRI) [[12, 13] will be used for semi-structured interviews (see Appendix 1 for script guide), with individuals involved in screening and presenting WARRIORS to patients, will take place across all sites (n=3-5 per site). Interviews with patients who decline randomisation will also be used to explore whether the patient information sheet or decision aid could be modified to enhance patient recruitment (script guide in Appendix 1). Interviews will be conducted by the trial monitor. Interviews will be recorded digitally and analysed following the conventions of thematic and the constant comparison approach [14, 15]. Summaries of pseudo-anonymised findings will be presented to WARRIORS principal investigators and to the TMG, including supporting evidence to describe factors hindering recruitment. A potential plan of action to improve recruitment will be proposed to facilitate decision making and define responsibilities for implementation.

5. PARTICIPANT ENTRY

5.1 Study Setting and Population

5.1.1 Inclusion criteria

- female sex
- age ≥50 years
- infra-renal abdominal aortic aneurysm with a maximum infrarenal aortic anterior-posterior diameter 4.0-5.4 cm, aneurysm, measured on ultrasonography or the centreline orthogonal diameter on Computed Tomography (CT) scan when this is the discovery imaging mode,
- Local assessment that arterial morphology is suitable for EVAR within manufacturer's IFU for any licensed infrarenal endograft, including those with concomitant common iliac aneurysm(s), provided the device is landed in the iliac arteries, without coverage of patent internal iliac arteries.
- Rockwood frailty score <7.

5.1.2 Exclusion criteria

- Male sex
- aneurysm of the infrarenal aorta of <4.0 or >5.4cm
- infrarenal aneurysm not meeting IFU for any specific licensed endograft for standard EVAR
- inability to give informed consent
- previous abdominal aortic surgery
- age <50 years
- concomitant thoracic aortic aneurysm of >4.0cm diameter
- excessive frailty (Rockwood score ≥7)
- life expectancy <2 years in the opinion of the investigator
- severe contrast allergy not amenable to steroid/antihistamine pretreatment (e.g., anaphylaxis)
- those considered unlikely to comply with follow-up
- concomitant common iliac artery aneurysm unless: a) the arterial morphology is within the IFU for standard infrarenal EVAR; or b) the arterial morphology is suitable for a licensed iliac branch device; or c) the internal iliac artery is occluded, and the stent limb can be landed in the external iliac artery without embolisation of the internal iliac artery.

These women with AAAs ≥4.0 cm diameter will still be eligible for inclusion in a parallel registry.

There will be no patient excluded as a result of geographical location, disability, gender, marriage and civil partnership status, ethnicity, religion or belief, sexual orientation, socioeconomic status or access to health or social care.

6. PROCEDURES AND MEASUREMENTS

6.1 Identification and Recruitment of Participants

Women with small AAA, 4.0-5.4 cm (based on local measurements by ultrasound) being monitored for AAA growth in hospital or community screening and surveillance programmes. Women also may be identified from imaging studies for other conditions, with referral to vascular surgeons, in which case the CT or other imaging measurement 9centre line orthogonal diameter) should be the entry criterion.

Trial centres will be vascular hubs/centres able to deliver both EVAR and surveillance programmes and have an annual EVAR caseload of ≥20 cases, with audited operative mortality of <3% for EVAR (via national registry or similar standard monitoring procedures).

The trial EVAR procedures will be delivered by vascular surgeons in accredited hospitals for vascular surgery in all participating countries.

6.2 Screening and Pre-Randomisation Evaluations

Participants will have a known AAA with diameter between 4.0 cm and 5.4 cm based on ultrasonography. Women will be assessed for Rockwood frailty score. Potential participants for the trial will have a CTA examination of the aorta, iliac and femoral arteries to assess inclusion and exclusion criteria (morphological eligibility for EVAR and presence of proximal aneurysms) unless a CTA has been completed within the previous 6 months. Prior to CTA examination, blood test for serum creatinine, cholesterol & haemoglobin should be performed. Potential participants will be screened to determine whether they meet all the inclusion criteria and none of the exclusion criteria listed for the trial. Sites will be asked to capture patient initials of each identified patient and to record the reasons for ineligibility. Women found eligible for the trial will be asked to complete the QoL questionnaires. Women who are ineligible for the trial will be enrolled into the registry for follow up.

Potential participants will be given information on the trial by local research staff when appropriate. They will be given a copy of the patient information sheet (PIS) and informed consent form (ICF). Translations in local languages will be available, as appropriate. Patients will be given at least 24 hours to read the PIS and consider their participation.

There will be an infographic or video explanation of the trial and a decision aid which has been developed specifically for this trial.

6.3 Randomisation and Blinding

Randomisation: 1112 women with small AAA will be randomised (1:1). Randomisation will be carried out using a web-based randomisation and Electronic Data Capture (EDC) system, called OpenClinica and women will be allocated to treatment using a variable block randomisation schedule, stratified

by country, age (≤75; >75 years) and aneurysm diameter (4.0-4.9; ≥5.0 cm). This will be generated by computer algorithm and released after checking patient eligibility and written consent.

Blinding: For ethical and practical reasons, patients and clinicians cannot be blinded to treatment allocation. However, the primary endpoint will be adjudicated by an expert panel (PROBE study - Prospective Randomized Open, Blinded Endpoint).

Table 6. Schedule of Activities

Procedures	**Screening**[a]	**Randomisation Day 0**	**AAA Repair**	**AAA Repair Post Op review (3 -12 weeks post op)**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Informed consent for trial and/or registry	X								
Height, weight & blood pressure	X								
Demographics	X								
Medical History	X								
Rockwood Frailty Score	X								
Serum creatinine, Cholesterol &Hemoglobulin	X[b]								
EQ-5D & HADS questionnaire	X[c]				X[j]		X[j]		X[j]
CT Scan with Contrast	X[b]			X[i]					X[k]
Randomisation		X[d]							
Pre-Operative Assessment[e]			X[h]						
Routine surveillance with imaging[f][g]					X	X	X	X	X
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X

Local clinical care teams should notify the trial manager if patients are withdrawn from active follow- up due to deteriorating physical or mental health or other reasons. Questionnaire follow-up also will be withdrawn but data linkage follow-up will continue. Registry patient follow-up for aneurysm events will be based on routine data only (e.g. NHS Digital or Medicare in the USA).

a. Patients found not eligible for the trial will be enrolled into the WARRIORS Registry.
b. Ony required if not performed within last 6 months.
c. QoL questionnaires to be given only to those found eligible for trial.
d. Patients will be randomised either to early EVAR or Surveillance group with SOC. Early EVAR should occur with 8 weeks of randomisation.
e. The pre-operative assessment will follow local SOC procedures.

f. Duplex, Ultrasound or CT scan according to local practice. Ultrasonographic surveillance is the preferred method since it is non-invasive, whilst being highly sensitive and specific, although in some countries (e.g. USA), CT, including non-contrast CT, may be used for surveillance

g. For Surveillance group, AAA between 4.0-4.4 cm diameter, annual surveillance can be recommended, increasing to every 6 months for AAA of 4.5 cm diameter or greater or according to current local practice and standard operating procedures.

h. Early EVAR should ideally occur within 8 weeks of randomisation. For the surveillance group, either EVAR or delayed AAA repair can be performed at any time if AAA growth is confirmed, or rupture is suspected.

i. CT only for those who undergo EVAR.

j. QoL and anxiety questionnaires may be conducted by telephone or video conferencing.

k. Exit CT scan required for those in surveillance group who have not had any AAA repair while on trial.

6.4 Follow-up

Follow up visits for trial patients will take place at each of the sites in a clinical examination room for interview, examination, and required questionnaires to be completed. The questionnaires are to assess quality of life (EQ-5D-5L) and anxiety (from HADS) before the 1, 3 and 5 year imaging assessment. Each study visit will be expected to take less than one hour including rest periods for the subject. For patients in the early EVAR group, follow up visits are likely to be preceded by imaging by Duplex or CT scan, to check continuing endograft exclusion of the AAA. Follow up for QoL and anxiety questionnaires may be conducted by telephone or video conferencing, which should precede the follow up imaging study. Data for aneurysm or other cardiovascular event treatments at hospitals not participating in the study will be collected from routine national health data sets (such as NHS Digital for English patients or Medicare in the USA).

Data will be collected on electronic case report forms using a study database hosted at Imperial College London.

7. CORE LABORATORY

7.1 CTA Specifications and Evaluations

The core laboratory must assess entry CT scans and pre-operative Scans in the surveillance group and exit CT scans of those without AAA repair at 5 years. Assessment of additional CT scans is optional and dependent on acquisition of additional funding for these.

Computed tomography angiography (CTA) of the whole aorta is the accepted gold standard to define the orthogonal maximum aortic diameter. It is also required for planning an endovascular aortic aneurysm repair (EVAR) and ensuring any repair is within the instructions of use (IFU) of the device intended to be implanted. It should be noted that CTA is an overarching technique of image acquisition and not a specific standard.

CTA is an enrolment requirement of this research study to ensure anatomical suitability. The study sites enrolling participants are anticipated to have considerable experience in performing and interpreting CTAs. There is however anticipated to be a considerable variety of acquisition CT scanners and techniques employed between and even within study sites. There will also be variability in the interpretation of the imaging obtained by CTAs. Variability in the interpretation is addressed by use of an independent Core lab analysis.

The total standardisation of imaging acquisition is neither possible, due to the variety of acquisition scanners that will be present in different sites, nor desirable (from a participant's perspective) as it may preclude the use of previous imaging that is adequate but not standardised and would therefore result in further exposure of the participant to ionising radiation and contrast medium.

Therefore, a minimum specification of resultant CTA imaging is given to ensure that images transferred to the Core Lab are of sufficient quality to allow independent anatomical assessment compared to inclusion criteria. Staff at individual study sites are expected to have greater familiarity with their local equipment and processes and are therefore best placed to implement CTA acquisition protocols to achieve this minimum specification. It is anticipated this specification would be met by the overwhelming majority of routine clinical scans carried out in study sites out with this research. An example CTA image acquisition protocol that is highly likely to achieve the

minimum specification are offered as suggestions to aid standardisation of acquisition. Members of the core Lab are also available to discuss with sites how to optimise acquisition.

7.2 Minimum Specification for CTA Imaging

7.2.1 Phases

A non-contrast scan (Prior to the administration of any contrast)
An arterial phase (Scan with contrast opacification of the aorta)

7.2.2 Extent of Scan

Both Phases must cover the arterial tissue from aortic valve to common femoral arteries i.e. between the Apex of the thoracic aortic arch cranially and the caudal extent of bilateral common femoral arteries (or the less trochanter of the femur). *In patients with a thoracic CT scan in the previous 6 months, the extent of the scan can be limited to diaphragm to femoral arteries to minimise radiation exposure.**

7.2.3 Contrast opacification

Increased opacification caused by iodinated contrast media must be present from the ascending aorta to the common femoral arteries.

7.2.4 Image Quality

Sufficient delineation of tissues both surrounding and within the aorta must be achieved without deleterious artefact being caused by denser materials found in the extent of the scan. With optimisation of windowing, aortic wall must be discernible from surrounding tissue, aortic lumen and/or thrombus must be discernible from aortic wall and blood/contrast must be discernible from thrombus wall at intended/likely EVAR seal zones.

7.2.5 Specification of image reconstructions to be transferred to Core Lab

Axial (to body axis) slices
Slice Thickness ≤1 mm
Slice Interval ≤ Slice Thickness - Slices should be contiguous (preferred) or overlapping.
Radiation dose & Tube setting data should also be transferred to core lab as a separate image if not coded in associated DICOM metadata.

7.3 Example CTA image acquisition protocol

IV Cannulation
Typically, in anterior cubital fossa to allow contrast injection at a rate of 5ml/s

Patient position
Supine with patient arms above their head

Scout scan
Mid Neck to proximal 1/3 of Thigh

Scan extent
Apex of thorax to most caudal lesser trochanter of Femur*

Non Contrast Scan
Full inspiration

Craniocaudal

Region of interest (monitoring slice) for Bolus Tracking
Descending thoracic aorta at level of carina.

Contrast Infusion
65-99 mL of non-ionic iodinated contrast with a 50ml saline chaser at 5 mL/s contrast injection considerations

Arterial Scan Trigger Threshold
Ideally dynamic patient specific peak opacification software
Otherwise usually ~ 150 HU + 4-8 seconds (scanner & trigger point dependent)
Contrast Scan
Full inspiration
Craniocaudal

kV and mA (these settings are typically scanner dependent)
Tube Voltage - ≥100kV (automatic tube voltage selection should only be deployed as part of an automatic exposure control that can also auto modulate tube current)
Tube Current - Automatic tube current modulation should be employed routinely, effective current should be set on local experience of resultant imaging quality.

Coverage speed
Dependent on detector array but coverage speed should allow MRP reconstruction with voxel size of ≤1mm.

Reconstruction
Iterative reconstruction when available
Default reconstruction should be the smallest slice interval detector array and coverage speed allow.
*Diaphragm to femorals in cases of recent thoracic CT scan, as above,

Pseudoanonymised DICOM CT data will be transferred to the core lab from site electronically or via CD. CT data from baseline and any subsequent pre-operative scans in EVAR or surveillance groups and exit CT at five years after randomisation for women with unrepaired AAA.

Data will be analysed according to a specific core laboratory protocol [16].

8. INTERVENTION

8.1 Endovascular Aneurysm Repair (EVAR)

The purpose of EVAR is to exclude the AAA from the circulation and therefore avoid the risk of future aneurysm rupture. Many different endografts are licensed and available (see Appendix 2). The TiDieR (Template for Intervention Description and Replication) checklist (Appendix 2), which includes a list of currently approved devices with IFU is provided as additional information. Newly approved devices will be added and any advances in technology tracked. The sizing of the aorta and planning of the operation should be conducted on a 3D workstation as standard.

A protocol for pre-operative care will be recommended and include pre-operative cardiac and anaesthetic assessments and prehabilitation advice based on the 2021 guidelines from the British Geriatric Society (https://www.bgs.org.uk/cpocfrailty). This includes advice about smoking cessation, alcohol, medication adherence (e.g. antihypertensives, statin as tolerated, antiplatelet)

and exercise [16,17]. Post-operatively, the recommended care will be according to European Society of Vascular Surgery 2024 guidelines [17]. All patients (early intervention and surveillance) also should be on medications to minimise cardiovascular risk (assuming them to be in a high-risk category, with management of smoking cessation, lipid levels etc according to European Society of Cardiology guidelines [17].

The procedure may be performed under general, local, or regional anaesthesia.

The purpose of the intervention is to reline the aorta and exclude the aneurysm from the circulation, to prevent further expansion and eventual rupture. With exclusion of the AAA from the circulation, the aneurysm sac should cease growth or decrease in diameter. Specifically in this trial the intervention will be performed when the aneurysm is between 4.0-5.4cm in size.

A strict protocol for the technical aspects of EVAR will not be given since practice around the world differs and patient differences necessitate a range of approaches. However, compliance with best practice guidelines for endovascular aortic aneurysm repair will be an expectation:

- Clinical practice guidelines EVAR: https://www.jvir.org/article/S1051-0443(10)00761-X/pdf
- Clinical practice guidelines AAA: doi: 10.1016/j.ejvs.2023.11.002. Epub 2024 Jan 23
- Clinical practice guidelines AAA: https://www.jvascsurg.org/article/S0741-5214(17)32369-8/fulltext
- Manufacturers' Instructions for Use

The procedure will take place in an operating theatre environment with mobile or fixed X-Ray imaging capabilities as per local standard operating procedures. Stent graft follow-up will take place at the institution where the index procedure was performed.

There are standards outlined for a dedicated EVAR Facility. These will be used as the gold standard in this study and provided to all participating units. For specifications please see: https://www.vascularsociety.org.uk/_userfiles/pages/files/Document%20Library/mhra_8pp_leaflet_amended_more_pages_web_version.pdf
Before the procedure, pre-operative CT imaging assessment will be performed and assessed for suitability for EVAR and must meet the minimum specifications set by the Core Laboratory (Section 7.2). The EVAR procedure will be performed based on local assessment of the pre-operative CT scan: these will be sent to the core laboratory for independent adjudication. The participant must be suitable for EVAR using any approved device within the manufacturer's instructions for use. The sizing and planning will take place on a dedicate 3D workstation.

Before EVAR, patients will be managed according to country-specific criteria (including a multidisciplinary team meeting in the UK) and undergo full pre-operative assessment. Each participant will be seen in the pre-operative assessment clinic with provision of participant information and supporting materials.

Pre-operative cardiac investigations will vary from country to country but should occur before EVAR.

Any further investigations will be ordered and treatment of conditions that might cause adverse outcomes during any operative procedure or delay recovery will be undertaken at the discretion of the treating team.

Prehabilitation advice will be recommended, based on guidelines from the British Geriatric Society.

Each patient will be consented for the EVAR procedure.

Access to the arterial system will be via the common femoral artery either using a percutaneous approach (closed with any of the available closure devices) or after surgical cut down and control of the artery.

Adjuncts to facilitate delivery of the EVAR device for participants with small iliac arteries, may include:

- Construction of a surgical conduit surgically to facilitate access.
- Balloon angioplasty and stenting of iliac arteries
- Construction of an ilio-femoral bypass
- Femoral or iliac endarterectomy +/- patch plasty
- Femoral or iliac patch plasty alone

The stent graft will be selected based on size measurements on the pre-operative CT scan. Each centre should only use the endografts with which they are familiar and use these within the manufacturer's IFU. A suitable oversizing of the graft as suggested by the instructions for use of the graft will be used.

Planned adjunct procedures may include:

- Endoanchor or endosuture placement
- Licensed branched iliac device
- Licenced fusion imaging software

When considering the landing zone of the stent, the clinician will plan to land the stent in the healthy parallel neck of the aorta just below the renal arteries, consistent with the necessary landing zone requirements of the chosen endograft. Balloon moulding will be considered if appropriate following stent graft implantation.

Distally the stent will may be landed in the common iliac artery or into the external iliac artery with management of the internal iliac artery.

At the end of the procedure post-stent intra-arterial digital subtraction quality control angiogram images will be obtained. Further imaging such as rotational CT analysis will be performed at the discretion of the investigator.

Unless expected to resolve by the initial post-operative scan, in the presence of any type 1 or 3 endoleak the operating team will undertake further procedures to attempt to rectify the endoleak based on local practice and equipment provision.

Any further adjunct procedures to treat endoleak will be placed in accordance with their instructions for use. Adjunct procedures may include one or more of (but will not be limited to):

- Repeat balloon moulding
- Aortic extension cuff
- Placement of a Palmaz (Cordis) balloon-expandable stent
- Iliac extension cuff
- Endoanchor or endosuture placement
- Chimney graft placement in the visceral/renal vessels

Post-operative care will conform to European Society of Vascular Surgery 2024 guidelines. The Enhanced Recovery After Surgery guidelines approved by the Society for Vascular Surgery will be circulated to all sites.

The participant will stay as an inpatient for standard post-operative monitoring and recovery,

before being discharged. Recovery and discharge arrangements will vary from site to site and should follow standard of care pathways at that site.

After discharge from the hospital after EVAR, patients will attend for CT scan at between 3 and 12-weeks, which is clinically necessary to assess the placement of the stent. Participants will attend for subsequent clinical and imaging (either with ultrasound or CT scanning) for stent graft monitoring as directed by local follow up arrangements, preferably based on the European Society for Vascular Surgery 2024 Clinical practice guidelines. These recommend limiting CT scans for the first post-operative and 5 year follow up only for low risk patients (the majority). Between these time points, ultrasound scans are recommended to minimise radiation exposure.

During the trial period modifications of the procedure and devices will be expected as new technology if developed. The procedural/device modifications will be tracked to ensure that the results of the outcomes from EVAR are not affected positively or negatively, leading to errors in the trial conclusions.

8.2 Ultrasound (or other imaging) Surveillance with delayed repair for rupture or aneurysm diameter reaching 5.5 cm threshold

All women will be monitored for AAA growth. Ultrasonographic surveillance is the preferred method since it is non-invasive, whilst being highly sensitive and specific, although in some countries (e.g. USA), CT, including non-contrast CT, may be used for surveillance. For AAA between 4.0-4.4 cm diameter, annual surveillance can be recommended, increasing to every 6 months for AAA of 4.5 cm diameter or greater or according to current local practice and standard operating procedures. For ultrasound surveillance, the anterior-posterior diameter should be measured in the longitudinal plane, since this is more repeatable than the transverse diameter. Calliper placement for measurements should be consistent at each surveillance visit. Outer-to-outer diameter measurements are preferred, but where sonographers are trained to measure either leading edge to leading edge or inner-to-inner diameters, these methods should be used and documented. When CT imaging is used for surveillance the centreline orthogonal diameter should be measured. When the diameter exceeds 5.4 cm the participant should have a prompt (target within 2 weeks) consultation with a vascular surgeon consideration of AAA repair by which ever method is recommended by the local team. The operation CRF should be completed, and the participant will then enter routine clinical follow up.

If there is any suspicion of AAA rupture, the patient must be admitted immediately as an emergency, preferably to a vascular surgeon the site where the patient has been followed up.

If there is a suspicion of impending rupture, with symptoms of back or abdominal pain referable to the aneurysm, further investigations should be performed, and consideration given to early elective repair. Thromboembolic evens referable to the aneurysm are also an indication for consideration of early elective (urgent) repair. (These conditions are known as symptomatic AAA).

All randomised patients will be offered smoking cessation advice and adjunct therapies as well as best medical therapy, including statins with a cardiologist-guided protocol (European Society of Cardiology guidelines for the high-risk category) [17]. This protocol will include and exercise, blood pressure, body weight and LDL-cholesterol targets and good diabetic control where relevant [17]. All patients will receive advice about exercise and physical activity. These measures and any incidental findings of hyperlipidaemia or poorly controlled hypertension will be reviewed by the vascular team and communicated to the patient using patient-facing educational resources as well as communication with their General/Family Practitioner.

8.3 Permanent Discontinuation of Study intervention and Withdrawal from Study

8.3.1 Permanent discontinuation of study intervention

Participants may discontinue study intervention for the following reasons:

- At the request of the participant.
- Adverse event/ Serious Adverse Event
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

8.3.2 Withdrawal from Study

Withdrawal from the study refers to discontinuation of study intervention and study procedures and can occur for the following reasons:

- Participant decision
- Loss to follow-up

8.3.3 Procedures for Withdrawal from Study

If a subject withdraws prematurely the reason for withdrawal will be recorded in the CRF/eCRF and medical records. All study visits up to the point of any planned withdrawal will be completed.

9. SAFETY REPORTING

9.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

9.1.1 Adverse Event Recording

Adverse events will be assessed at each study visit. The following will be assessed for all adverse events:

- *date of onset*
- *description of event*
- *frequency*
- *severity*
- *causality*
- *outcomes*
- *action taken.*

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the follow-up visit, whichever is the sooner.

Adverse events that are not serious adverse events will only be recorded on adverse event forms if the adverse event either occurs within 90 days of the index AAA repair or is aortic related. The following will be noted as aortic related events:

- Any events within 30 days of index repair
- Access vessel dissection or rupture
- Buttock claudication
- Endoleak
- Graft kinking (clinically significant)
- Graft migration of >5mm
- Graft limb thrombosis/stenosis/occlusion
- Limb ischaemia or toe amputation
- New onset claudication
- Pseudo-aneurysm at graft insertion site
- Surgical site infection

All SAEs will be recorded throughout the study.

9.1.2 Severity of Adverse Events

The assessment of severity will conform to the following definitions:

- Mild: Awareness of event but easily tolerated
- Moderate: Discomfort enough to cause some interference with usual activity
- Severe: Inability to carry out usual activity

9.1.3 Causality of Adverse Events

The assessment of causality will conform to the following definitions:

- Unrelated: No evidence of any causal relationship
- Unlikely: There is little evidence to suggest there is a causal relationship and there is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
- Possible: There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
- Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

9.2 Serious Adverse Events (SAE)

An SAE is defined any untoward medical occurrence or effect that:

- Results in death;
- Is life-threatening (e.g. aortic rupture)*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation (eg graft infection or conversion to open repair)**;
- Results in persistent or significant disability or incapacity (e.g. major limb amputation);
- **Is a congenital anomaly or birth defect**

** "Life-threatening" in the definition of "serious" refers to an event in which the participant 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.*

*** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).*

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 participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

9.2.1 Reporting of SAE's

Reporting of all SAEs, occurring during the study must be performed as detailed in the study-specific Safety reporting instructions.

Active monitoring of all participants after the end of the trial is required clinically but not as part of this study. If the investigator becomes aware of safety information that appears to be related to the trial, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality. Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

Reporting of all SAEs to the Sponsor is not required, **unless they are related and unexpected.**

I. Related SAEs

Related: resulted from administration of any of the research procedures. Expected SAEs are detailed in the study-specific Safety reporting instructions.

II. Unexpected SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence

III. Reporting of SAEs that are related and unexpected.

SAEs that are *related and unexpected* should be notified to the relevant REC and the Sponsor in accordance with local requirements. For Imperial-Sponsored studies related and unexpected SAEs must be reported to the Sponsor within 15 days of the investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor (RGIT@imperial.ac.uk) of all related and unexpected SAEs.

Follow up of participants who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Reports for related and unexpected SAEs should be unblinded prior to submission if required by national requirements.

9.3 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CIs/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

Please notify the trial of SAE's: warriors@imperial.ac.uk

10. STATISTICAL ANALYSES

10.1 Sample Size and Power Considerations

The samples size has been calculated to be 1112 patients (556 in each arm), followed up for 5 years. This was estimated after reviewing available data from published registries, source data from SWAN project to assess the cost-effectiveness of screening women for AA [ref HTA report] and previous RCTs, particularly the UK Small Aneurysm trial [20]. The events included in the primary outcome are death within 30 days of intact AAA repair, death within 30-days of re-interventions following AAA repair and AAA rupture (fatal and non-fatal). Table. Summary of events per 100 women over 5 years for the sample size estimation./.

Event	Early EVAR	Surveillance	Notes for surveillance
% undergoing intact AAA repair	98% estimated	55%[20]	From previous RCTs AAA growth rate has not changed over time
Operative mortality for intact AAA repair	1.5[5,910]	2.48[6,8,22,23]	Mean mortality 4.5% (older women) 50% EVAR, 10% complex EVAR, 40% open repair
Death after late complications of aneurysm disease/repair	0.7[21]	0.55estimated	Larger AAA, older patients, more complex EVAR giving higher complication rates[22,24-5]
AAA rupture (~80% fatal)	0.2[21]	4.2 [20,27,28]	Rupture rate 1.5 per 100 woman-years[27]. Could be higher[20,28]
Total	2.4%	7.23%	

10.1.1 Primary endpoint incidence in the early EVAR group

The estimate of 1.5% operative mortality is taken principally the Vascular Quality Initiative (VQI) and other USA registries, where the repair of small AAA is more common than in Europe, reported [5, 18]. The USA arm of the trial will run via the VQI, where a recent VQI study has reported that the operative mortality of small AAA is less is likely to be ~0.5% [5]. The data for mortality attributable to either the complications of AAA repair or within 30- days of reintervention come from the EVAR-1 and other trials of EVAR versus open repair but may be lower for small AAA [19]. Nearly all women in this group should undergo EVAR within a target of 8 weeks from randomisation but delays for medical reasons will occur in a few patients, resulting in an overall risk of death from AAA rupture of 0-2% 5-years in the early EVAR group. This gives a primary endpoint incidence of 2.4% in the early EVAR group.

10.1.2 Primary endpoint incidence in the surveillance group

The estimate of 55% of women undergoing repair of AAA by 5 years derives from the UK Small Aneurysm Trial, supported by the other RCTs of early repair versus surveillance. Since the women, at the time of repair, will have larger AAA than the early EVAR group, it is estimated that only half will be suitable for an endovascular repair and half will receive either open or complex endovascular repair. The women also will be older at the time of AA repair than in the early EVAR group. The

operative mortality estimates for EVAR, complex EVAR and open repair are 2.4%, 8-10% and 6% respectively [6 8,22,23], giving an overall operative mortality of 2.48%. Complication and reintervention rates also increase markedly with age and AAA diameter [24,25], so that deaths from the late complications of repair also are increased versus the early EVAR group, with most reinterventions occurring within the first 18 months of repair [19]. The risk of AAA rupture increases with increasing aortic diameter. An earlier modelling study indicated that the risk of rupture of a 4.2 cm AAA in women was 1%/year [3]. More recently the SWAN project estimated that the rupture risk for women with AAA (4.-5.5 cm diameter was 1.5 per 100 person years [20]. A Swedish study has indicated that after 5 years 9.7% of women with unrepaired AAA had died from AAA rupture, whilst in the UK Small Aneurysm Trial 7/93 (7.5%) women in the surveillance group had died of AAA rupture by 5 years [21, 22]. After accounting for the increasing proportion of women likely to undergo elective repair in the later years of the WARRIOR trial, an overall rupture rate of 4.2% in the surveillance group appears to be a relatively conservative estimate. This gives a primary endpoint incidence of 7.23% in the surveillance group after 5 years.

10.1.3 Sample size calculation

Considering that many of the above estimates are based on registry study data and the event rate might be lower in the context of a randomised trial we have considered a conservative estimate of 6.2% primary event incidence for the surveillance group versus 2.4% in the early EVAR group f in the sample size calculation.

The sample size calculation was performed according to the cause-specific hazard (CSH) approach [23]. Therefore, assuming an event rate at 5-years of 6.2% in the surveillance group, with 3-years recruitment and 5-years follow up, accounting for a competing risks of non-AAA related death of 35% in both groups and a proportion of patients lost to follow-up during the entire study of 0.05, a sample size of 446 patients per groups will give 90% power with two-sided alpha 0.05 to detect an hazard ratio of 0.376 (6.2% vs 2.4%) allowing for 5% attrition. Allowing for 10% total crossovers, a sample size of 1112 patients has 90% power to detect the same, but if crossovers are scant, we can detect an HR of 0.422 (6.2% vs 2.67%) and 80% for HR 0.482 (6.2% vs 3%).

10.1.4 Sample size for QALYS

Given the scarcity of data to support the estimation, the pragmatic approach previously used for surgical trials where supporting data were lacking is being used [29]. The potential limitation of response rate to questionnaires (EQ5D-5L) and questionnaire fatigue will be addressed by offering small denomination shopping vouchers, (or opportunity for charitable donation,) for form completion. This increased the response rate to 85% at 3 years in a previous AAA trial based in the UK and Canada [30].

The minimum clinically significant difference (MCID) in response to the EQ5D-5L is 0.07 [24]. Using the estimate for the standard deviation of 0.22 (based on source data for women from the EVAR-2 trial [25]), this study is powered to detect a difference of 0.046, and therefore has >95% power to detect the MCID between groups.

10.1.5 Planned subgroup analyses

To investigate a possible recommended level of the diameter threshold for intervention, a subgroup analysis by baseline diameter (or ASI) will be performed. Countries with recruitment

targets of over 120-150 patients may consider country-specific cost- effectiveness modelling: this will include the UK. The key cost drivers including length of stay in the operating theatre, length of stay on intensive or enhanced support units and total length of hospital are being collected on the operations details case record form. Other cost data will be derived from routine local sources.

10.1.6 Bias

In this trial bias could be introduced if individual centres use more selective criteria for inclusion in the trial or fail to retain patients in the surveillance group. The former has been partly addressed by the stratification of randomisation and comparison with patients entered into the registry, whilst the latter can be minimised by careful selection of centres for the trial. Prior to participation, centres must confirm clinical equipoise and have agreed to treat women in line with the protocol. Internationally, different health systems will require different strategies to prevent patients undergoing surveillance being treated with early EVAR in another centre, for example in the USA, centres that are part of integrated health systems may retain patients more effectively. This is not as great a concern for the UK.

10.2 Statistical Analysis

The analysis and reporting will conform to the standards set by the Consolidated Standards of Reporting Trials statement.[26] Analysis will be undertaken guided by a pre-specified statistical analysis plan, which will be reviewed by the DMEC and approved by the TSC, prior to database lock. Any deviations from the SAP will be justified and documented in the final report.

10.2.1 ANEURYSM RUPTURE & AAA-related MORTALITY

We will complete all analyses according to a pre-defined statistical analysis plan, based on the intention-to-treat principle, with outcomes assessed from the time of randomisation. Our research question is if the intervention, that targets a specific set of patients in a specific range of AAA diameter, would reduce the rate of patients having an AAA-related event (while they are still at risk).

The primary endpoint of AAA related mortality including non-fatal ruptures will be analysed using survival analysis according to the cause-specific hazard approach. We will consider non-AAA related mortality as competing risk. From an estimand perspective, non-AAA deaths are intercurrent events and will be handled with a “while alive” strategy, to be censored as competing events in the analysis.

For the primary analysis, the relative cause-specific hazard of early EVAR versus surveillance for AAA-related mortality/rupture will be estimated using cause-specific proportional hazards model, where other deaths are competing events, including treatment and stratification factors (age, and aneurysm diameter) as fixed effects and country as either random or fixed effect. Proportionality assumption will be checked and piecewise hazards (with cut-point at 1, 3 and 5 years) or flexible parametric models will be used in case of failure of the proportional hazards assumption.

Cumulative event probabilities for primary outcome of AAA related mortality will also be estimated using nonparametric cumulative-incidence function estimator.

Secondary (or sensitivity) analysis of the treatment effect will be estimated using the Fine and Gray sub-distribution hazard model.

Secondary analysis will also include re-analysis of outcomes using aortic size index (ASI maximum aortic diameter divided by body surface area). Subgroup analysis by baseline diameter (or ASI) will be performed including an interaction between baseline diameter (or ASI) as continuous variable and treatment group in the survival model[20]. To take into consideration possible non-linearity, a fractional polynomial interaction approach will be used.

The secondary endpoint of QALY over 5-years, will be compared between EVAR and surveillance group using linear regression adjusted for baseline QoL score and stratification variables. Other outcomes will be analysed using the appropriate generalised linear model or mixed model according to the distribution of the outcome.

All analyses will follow the intention to treat (ITT) principle, unless otherwise specified and two-sided 5% significance level will be used. Additional per protocol analysis will also be performed excluding subjects with major deviations. A detailed statistical analysis plan will be reviewed by the TSC and finalised prior to database lock.

10.2.2 Rationale for selection of a cause-specific hazard approach

In the competing risk setting, two approaches, the cause-specific hazard function and the cumulative incidence function, are commonly used to summarize outcomes by event type. Inferential results for tests based on these different metrics can differ considerably for the same cause-specific end point. Depending on the questions of principal interest, one or both metrics may be appropriate to consider.

Cause-specific hazard ratio (csHR) estimates the direct effect of the treatment/covariate on instantaneous risk of the primary event for those at risk; whereas sub-distribution hazard ratio (subHR) reflects a combination of the treatment's effect on the primary outcome and on the competing risk because both of these effects impact the probability of observing the primary event by a given time.

There will be an analysis for safety (30-day operative mortality), feasibility (recruitment rate) and data completion at the end of the Vanguard trial. These data will be used to enable the DMEC to re-set stopping rules for the remainder of the trial. Since AAA- related events will mainly occur early on in the group randomised to early EVAR but later, at an increasing rate, in the surveillance group, there is no value in pre-specifying any further interim analysis until at least an average of 3 years follow-up have
accrued. Nevertheless, the DSMB will monitor event rates in both groups for safety. After half of the patients reached the maximum follow up, there will be an interim analysis for futility (inability of the trial to provide meaningful clinical
information). Therefore, sponsors can be reassured by 2 checkpoints to minimise unnecessary funding support.

10.2.3 Health-related Quality-of-Life (QoL)

Health-related quality of life will be measured according to a generic measure, the EQ-5D, which

requires patients to describe their health on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. We will consider the EQ-5D with 5 levels (EQ-5D-5L) which for each dimension requires patients to state whether they have 'no problems', 'slight problems', 'moderate problems', 'severe problems', or 'extreme problems/unable'). Each patient's described health status at each timepoint will be valued according to health state preferences from the general population of each individual country to calculate EQ-5D utility scores, which are anchored on a scale from 0 (death) to 1 (perfect health). If health state preferences are not available for a particular country, this will be taken from the UK. The mean EQ-5D-5L at 1-, 3- and 5- years post-randomisation will be compared between the randomised groups, as above.

10.2.4 Quality-Adjusted Life years (QALYs)

Quality adjusted life years (QALYS) will be calculated by valuing each patient's survival time by their EQ-5D-5L scores at 1, 3 and 5 years according to the 'area under the curve' approach. For survivors, QALYs will be calculated using the EQ-5D-5L scores at baseline, 1-, 3-, and 5-years, assuming linear interpolation between the different time points. For decedents at any point between randomisation and 5-years, we will use a linear interpolation between the last available EQ-5D-5L measurement and the date of death, at which point a zero EQ-5D-5L will be applied and contrasted between groups, as above.

10.2.5 International Analysis of Cost-effectiveness

These analyses are fully funded by the British Heart Foundation, United Kingdom, the Novo Foundation, Denmark. Analyses will be conducted by Dr M Gomez, (University College London,) and Professor R Sogard, (University of Southern Denmark).

Total discounted costs at 5-years will be estimated by valuing the observed resource use with local unit costs and discounting rates, converting the cost into purchasing power parities (PPPs) adjusted Euros, inflating the costs into the latest available common price year using the general consumer price index and, finally, discounting at the recommended local rate. The PPP avoids the impact of short-term currency fluctuations and recognised the relative purchasing power across different countries. In the base case, incremental, discounted costs and discounted QALYs will be reported as, mean differences between randomised arms, together with 95% confidence intervals. The differences in average costs and QALYs between the randomised groups will be used to estimate the Incremental Net Monetary Benefits (INB) as the QALY gain multiplied by different values for a range of hypothetical willingness to pay thresholds (WTP) for a QALY gain (to be discussed with international stakeholders) and subtracted from this the incremental cost. INBs will be reported overall, and for the same pre-specified subgroups as for the clinical endpoints. An incremental net benefit greater than zero suggests the intervention is cost-effective at a specific WTP threshold. The uncertainty around the differences in average costs and QALYs between the randomised groups will be illustrated on the cost-effectiveness plane. To express the uncertainty in the joint estimation of the incremental costs and QALYs, we will consider non-parametric bootstrap. We will also report cost-effectiveness acceptability curves, by calculating the probability that, compared to Routine Surveillance, the Early EVAR strategy is cost- effective, at alternative levels of willingness to pay for a QALY gain. As a supplement to the main results, individual-country results will be analysed and based on observed EQ- 5D, survival time and resource use, which is valued using country-specific weights for QALY, unit costs, inflation rates for common price

year and discount rate (no PPP adjustment). Relevant sensitivity analyses will be conducted for the main results with respect to unit costs, discount rate and eventual extreme observations as a minimum.

10.2.6 The Quintet Recruitment Study

The qualitative recruitment study will be analysed using the Q-QAT technique of interview transcripts (https://doi.org/10.1186/s13063-015-0617-1). This will quantify time spent explaining aspects of the study providing useful indications of the order of presentation and degree of balance between WARRIORS interventions, the time WARRIORS is first mentioned and time devoted to it. Trial documentation may be reassessed in the light of the recruitment process findings.

11. REGULATORY, ETHICAL AND LEGAL ISSUES

11.1 Decalration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the seventh revision (2013) of the 1964 Declaration of Helsinki.

11.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

11.3 Research Ethics Committee (REC) or Institutional Review Board (IRB) Approval

11.3.1 Initial Approval

Prior to the enrolment of participants, the REC or IRB must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

The Study Coordination Centre has obtained approval from the Liverpool Central Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation. Data and all documents relating to such amendments will be stored for a minimum of 10 years after closure of the study.

Amendments may need to be submitted to the Funder for review prior to REC submission.

11.3.3 End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines. The end of trial notification will be submitted within 90 days of the end of trial definition being met.

11.4 HRA Approval in the UK

In England, Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

In other countries all similar, relevant approvals will be necessary.

11.5 Other Required Approvals

Investigators must ensure that all procedures that take place as part of the trial (either early EVAR or late interventions due to AAA expansion or complications) are compliant with the relevant Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

In the event an extension is required, the relevant approvals will be sought.

11.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU QA Manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made. A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol,

which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

11.7 Insurance and Indemnity and Sponsor

The Sponsor has civil liability insurance, which covers this study in all participating countries. Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

11.8 Trial Registration

The study has been registered on a trial database (clinicaltrials.gov in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

11.9 Informed Consent

The investigator is responsible for obtaining written informed consent from the subject, providing an adequate explanation of the study's aims, methods, anticipated benefits, and potential hazards before any trial procedures begin.

Consent will also be obtained for participant's contact details to be shared with the central study team for the purposes of future long-term follow-up and optional dissemination of trial results. 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, either on paper or electronically.

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.

There will be a separate consent but with the same criteria as above for the recruiting staff from the clinical care team and patients who decline to participate in the trial, for participation in the Quintet Recruitment study.

11.10 Contact with General/Family Practitioner

It is the investigator's responsibility to inform the participant's General/Family Practitioner (where applicable) by letter that the participant is taking part in the study provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

11.11 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, participants will be identified by a participant 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 participants' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Health Authorities, Regulatory Authorities and RECs.

Research staff will have access to participants' personal data. The Trial Monitor from Imperial Clinical Trials Unit will have access to view personal records for monitoring purposes (source-data verification, eligibility and existence verification) during monitoring visits. No person outside the clinical care team can have access to identifiable information without consent for the study being in place.

The Sponsor (Research Governance and Integrity Team, Imperial College Academic Health Science Centre) and other regulatory bodies will also have the above access if conducting an audit of this study. This is mentioned in a statement on the participant consent form and participant information sheet.

Only pseudo-anonymised or anonymised data will be transferred outside of the trial team. Such transfers will include data for the core CT laboratory at St George's Hospital London, to the health economists (Dr Gomes at University College London and the University of Southern Denmark), and to the qualitative recruitment specialist Dr Evley at the University of Leicester. The trial monitor will conduct the recruitment surveys and Dr Evley will receive the pseudonymised data for interpretation. Pseudonymised data also may be shared with the principal trial funder, the British Hear Foundation.

Some anonymised data also may be shared with commercial funding partners (Medtronic and Terumo Aortic) for the purposes of research, education, to monitor use and safety of their products only. Such data will include patient age, body mass index, details of the operation and its possible complications and CT measurements and images of the aorto-iliac vessels.
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

11.12 Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the trial manager/Imperial Clinical Trials Unit.

11.13 Payments and Incentive

Individual researchers will not receive any payments or incentives for taking part in this research, over and above their usual salary.

For patient participants in the trial, the potential limitation of response rate to questionnaires (EQ5D-5L) and questionnaire fatigue will be addressed by offering small denomination shopping vouchers, (or opportunity for charitable donation,) for form completion. This increased the response rate to 85% at 3 years in a previous AAA trial based in the UK and Canada

11.14 End of Trial

The end of the trial will occur when the final participant has completed the final follow up visit and all trial data have been captured on the trial database, and the database locked.

11.15 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given 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.

12. DATA MANAGEMENT

12.1 Source Data

All written or electronic patient health records held by the hospital or general/family practitioners or other medical facility.

12.2 Language

eCRF's will be in English, with translated examples available for use in non-English speaking countries. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

12.3 Database

Trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the OpenClinica database. Data is entered into the EDC system by trained site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her appropriate designee. All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF manual.

12.4 Data Collection

Details of procedures for CRF/eCRF completion will be provided in a study manual. Data from all trial visits will be collected and entered on the trial eCRF built in the OpenClinica system. Details of procedures for eCRF completion will be provided in a study manual.

12.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

13. STUDY MANAGEMENT STRUCTURE

13.1 Trial Steering Committee

An international Trial Steering Committee (TSC) will be convened and a minimum quoracy for any meeting to conduct business is 60% (three fifths) of the appointed membership. Independent members must make up a minimum **of** 60% of the TSC membership.

Membership should comprise an Independent Chair, an independent statistician or other person with expertise in the main methods used in the study, at least one public member, preferably independent. Others with clinical or other expertise relevant to the project, such as in health economics, social care, public health can also be included. Ideally, the TSC should invite observers, including representatives of the sponsor and research network as well as two PPIE representatives to meetings.

TSC meetings should be scheduled to follow shortly after DMEC meetings so that reports from the DMEC can be considered, if appropriate. Minutes of meetings should be sent to all members, the sponsor, and the funder, and be retained in the TMF.

The responsibility for calling and organising Steering Committee meetings lies with the Chief Investigator, in association with the Chair.

The Funders (including the British Heart Foundation) reserves the right to attend any meeting, and therefore should be included in relevant invitations.

The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter (See CR014).

13.2 Trial Management Group

Each country will have a Trial Management Group (TMG). In the UK, this will include the Chief Investigators, co-investigators and key collaborators, trial statistician, trial manager and two lay representatives. In the UK, the TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference. (See CR014). One to two lay people will be included. Outside the UK, the country TMGs should be composed of the country principal investigator, co-investigators, representative(s) from national professional society, country trial co-ordinator and patient or lay representative.

13.3 Data Monitoring& Ethical Committee

Membership of the Data Monitoring and Ethical Committee (DMEC) will be small (3- 4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert statistician. Membership may include members of the public.

All DMEC members are to be independent (with at least one member being UK based and/or holding a substantive UK based appointment).

The DMEC charter will be based on the DAMOCLES study group template. Its roles will include: monitoring the data (including interim analyses) and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; reviewing the interim analyses; advising the TSC regarding the release of data and/or information; and considering data emerging from other related studies. Refer to the separate DMEC charter for further details (See CR014).

13.4 Endpoint Committee

There will be an independent committee to adjudicate the primary outcome of AAA-related mortality and rupture. The committee will consist of international experts and will be chaired by a non-surgeon cardiovascular specialist (e.g. cardiologist).

13.5 Early Discontinuation of the Study

The DMEC will define the criteria for early discontinuation and make recommendations to the TSC as required.

13.6 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Trial Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

13.7 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy, and consistency of the data. Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

13.8 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and for the UK, the NHS Research Governance Framework for Health and Social Care (2nd Edition) and similar regulations in other countries.

13.9 Peer Review

The peer review conducted for the study has been through the Global Cardiovascular Research Funders Forum and the principal funder, the British Heart Foundation. The trial has also been reviewed by serval international committees and senior members of ICTU and researchers at Imperial College London.

13.10 Patient and Public Involvement and Engagement

Involvement of PPIE to Date

During the inception of the trial design, an initial mixed-gender group of participants (7 women and 5 men) spanning socioeconomic and ethnic backgrounds reflective of the AAA population was recruited with inclusion of carers (and/or close family members) to enable consideration of more vulnerable patient's views. Verification of the importance and acceptability of the trial was confirmed, and advice was provided regarding GCRFF funding application and future patient and public involvement. The PPIE panel confirmed that the lived experience of men and women with

an AAA were different and therefore future patient and public involvement for the WARRIORS trial should more explicitly explore the unique needs, specific priorities, and perceptions of women with an AAA to provide a sensitive and effective trial design. Further work to assess trial acceptability and establish participant priorities has also been conducted in Germany, Sweden, Canada and the USA.

Following on from this in the UK, the dedicated PPI group was expanded to include a larger cohort of 23 women (and their carers and/or close family members). These women were selected to have had varied experience of the full spectrum of AAA repair from different centres. They were either pre-operative with a small AAA under surveillance (n=12) or had received a mixture of endovascular (n=7) or open (n=4) repair, of which some had experienced an emergency repair and/or had experience complications from repair. In-depth one-to-one interviews were conducted with 18 of the PPIE panel. These members provided information regarding their personal lived experience, priorities, anxiety and concerns regarding repair, potential barriers to recruitment and retention and opinions regarding trial design and utility which were used to shape the application. They also reviewed the lay summary and initial drafts for proposed patient facing resources.

Plans for On-going and Future PPIE

INVOLVE principles of consultation and collaboration will be employed to ensure that research is conducted with those affected, that acceptable methodology is utilized, relevant outcomes are measured, resources are used appropriately, and to enable patient engagement (https://www.invo.org.uk/wp-content/uploads/2013/12/INVOLVE-Principles-and-standards-for-public-involvement-1-November-2013.pdf).

Recruitment

PPIE members may constitute women or men who have undergone, or care for someone who has undergone, AAA repair, with the aim to span socioeconomic and ethnic backgrounds reflective of the AAA population. Two PPIE representatives will be selected from each participating country to participate in an international PPIE group, which will meet virtually on an annual basis. From this group, two members with PPIE experience will be selected to act as lead and two PPIE representatives will also be selected to act as non-voting members to contribute to the TMG and TSG. We have identified that many AAA patients and their families may have individual communication needs including visual or hearing impairments, a language barrier or digital illiteracy. As such a diverse approach to inform PPIE participants of study progress will need to be employed, such as inclusion of relatives or carers for support, use of translators for meetings as necessary and one-to-one updates regarding trial progress. *Training and Support*
The dedicated PPI panel will receive training on the project background, as well as in PPIE. Support will be given to facilitate members with specific needs to participate, such as IT training and text translation for the hearing impaired. Meeting agendas and supporting information will be given prior to events, which occur at appropriate time and intervals, with members given the opportunity to provide individual one to one feedback or anonymous feedback to improve the collaborative process. Additional support and safeguarding principles are applied in consideration of the emotional impact of discussing AAA repair with participants who may have suffered from adverse outcomes themselves.

Members will be remunerated for their time and expenses, with additional costing for Wi-Fi, use of translators and support from carers. Due to the international nature of the trial and to mitigate the risk of COVID-19, meetings will be virtual, with real-time text translation. Handling of PPIE

participant information will be conducted at ICTU according to GDPR (general data protection regulation).

Planned PPIE Input

Consultation and collaboration with the PPIE group will be conducted at regular intervals to co-produce resources and guide the trial as a whole. Identified key areas vital for PPIE input include:

1. Appraisal of project design – acceptability of patient assessments and identification of potential barriers to successful recruitment or retention.
2. Co-production of patient-facing resources (e.g., lay summary, decision aid, patient information sheet, website, video and consent forms).
3. Contribution to trial management through lead PPIE member participation in steering/advisory group meetings.
4. Contribution to trial reporting through prioritization of the relevant results. Co-development of engagement resources for dissemination. The associated PPIE panel will advise on the best strategies to ensure the results reach a wide section of the relevant population including underserved groups, who may have individual communication needs including visual or hearing impairments, a language barrier or digital illiteracy. The PPIE panel also will provide input into a short, animated video reporting final trial results aimed at the general population, which will be available on the trial website and on You-tube.

Measurement of Impact

Evaluation and reporting of PPI impact will be conducted using the PiiAF (Public Involvement Impact Assessment Framework) and through feedback and reflections, which will then be reported in publications utilising the GRIIP2 (Guidance for Reporting Involvement of Patients and the Public) checklist.

13.11 Publication and Dissemination Policy

Informing and engaging patients/service users, carers, NHS, social care organisations and the wider population: The dissemination strategy for our findings will be aimed at reaching the largest possible stakeholder audiences. We will maintain and develop the trial internet site, initially used as a public and participant information tool, to disseminate our findings.

On completion, we will produce an executive summary of our findings to be distributed to relevant policymakers, and the guidelines committees of the European Society of Vascular Surgery and Society of Vascular Surgery.

We will aim to present the findings from the study to the Vascular Society, British Society of Endovascular Therapy, American Heart Association and the European Society of Vascular Surgery. We will aim to publish the findings of the trial in widely disseminated high impact academic journals. We will make our intervention methodology and results available through presentations, workshops, conferences, the website, working papers and journal articles.

The Consort Guidelines and checklist will be adhered to with regards any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals (http://www.consort-statement.org/).

For Patients/Public: We will produce a short, easy to understand summary of our research findings (written and as a short video) that will be available from our website and that will be sent out widely

to patients and the families of patients with aortic dissection and the wider population via national patient organisations (such as AAAUK), charities (such as the Circulation Foundation) and relevant professional societies (Vascular Society, European Society of Cardiology, American Heart Association). Our PPI panel will advise on the best strategies to ensure the results reach a wide section of the relevant population including underserved groups. In addition, we will hold a webinar for patients and carers to disseminate the results.

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.

It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results, and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Release data will be subject to a data use agreement between Imperial College London and the third party requesting the data. The data use agreement must detail agreed use and appropriate management of the research data to be shared. We will promote appropriate acknowledgement of the significant contributions of all parties to creating new value through data-sharing, including the researchers who generated the data and the original funder (the BHF).

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

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REVISION HISTORY

Version	Date	Summary of changes
0.1	November 2023	First version
1.0	4th June 2024	Approved by Imperial Research Governance for Ethics Submission
2.0	1st May 2025	• Change of CI from Professor Janet Powell to Professor Colin Bicknell and update of Anna Louise Poncey as Co-lead. • Addition of Trial Manager Contact Details • Table 2 and 4 Reformatted. • Clarification to Figure 1: Study Flow Chart • Clarification to section 6.2 which blood tests should be performed. • Update to section 6.2 that QoL questionnaires are administered only to patients eligible for the trial. • Update to Table 6: Schedule of activities • Removed mention of MRI for post-EVAR 3–12 week follow-up from Section 8.1, as this is not SOC • Removed X-ray and ECG from Section 8.1 regarding pre-operative investigations. Procedures should follow the standard of care according to local practices. • Update to section 11.9 that consent must be taken before any study procedures commence. • Removal of mention of Annual Progress reports to REC as they are no longer required. • Reformatting of headers and sections • Correction of minor typographical errors and duplications.

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

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

Study Title: Women's Aneurysm Research: Repair Immediately or Routine Surveillance, Trial and Registry

Protocol Number: 24CX8836

Signed: 

Colin Bicknell
Chief Investigator

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

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

Study Title: Women's Aneurysm Research: Repair Immediately or Routine Surveillance, Trial and Registry

Protocol Number: 24CX8836

Signed: Ruth Nicholson Digitally signed by Ruth Nicholson Date: 2025.06.09 10:34:01 +01'00'

Ruth Nicholson
Head of Research Governance and Integrity
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

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

Study Title: Women's Aneurysm Research: Repair Immediately or Routine Surveillance, Trial and Registry

Protocol Number: 24CX8836

Signed: Emanuela Falaschetti Digitally signed by Emanuela Falaschetti Date: 2025.06.06 12:47:16 +01'00'

Emanuela Falaschetti
Senior Statistician
Imperial College London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL 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.

Study Title: Women's Aneurysm Research: Repair Immediately or Routine Surveillance, Trial and Registry

Protocol Number: 24CX8836

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES

- Appendix 1: Quintet Recruitment Intervention Study for WARRIORS trial. Script guide for semi- structured interviews
- Appendix 2: TiDieR (Template for Intervention Description and Replication) checklist
- Appendix 3: Table of approved EVAR device specification