IMPERIAL

EARNEST	**Protocol No: 174766**	**Sponsor: Imperial College London**	**V1.0 7th Oct 2024**

CLINICAL STUDY PROTOCOL

(ICTU ADOPTED)

Full Study Title: Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST): A randomised trial to assess the clinical and cost-effectiveness of thoracic endovascular aortic repair in the subacute phase after uncomplicated type B aortic dissection.

Short Study title / Acronym: EARNEST

Sponsor: Imperial College London

Version no: 1.0

Protocol Date: 7th October 2024

Funder acknowledgement and disclaimer statement:

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This protocol has regard for the HRA guidance

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This protocol describes the EARNEST 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
CRF	Case Report Form
CT	Computerised Tomography
CTA	Computerised Tomography Angiography
DMEC	Data Monitoring and Ethical Committee
eCRF	Electronic Case Report Form
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ITT	Intention to Treat
LSHTM	London School of Hygiene and Tropical Medicine
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QRI	Quintet Recruitment Intervention
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SURV	Surveillance
TBAD	Type B Aortic Dissection
TEVAR	Thoracic Endovascular Aortic Repair

TMG	Trial Management Group
TSC	Trial Steering Committee
uTBAD	Uncomplicated Type B Aortic Dissection

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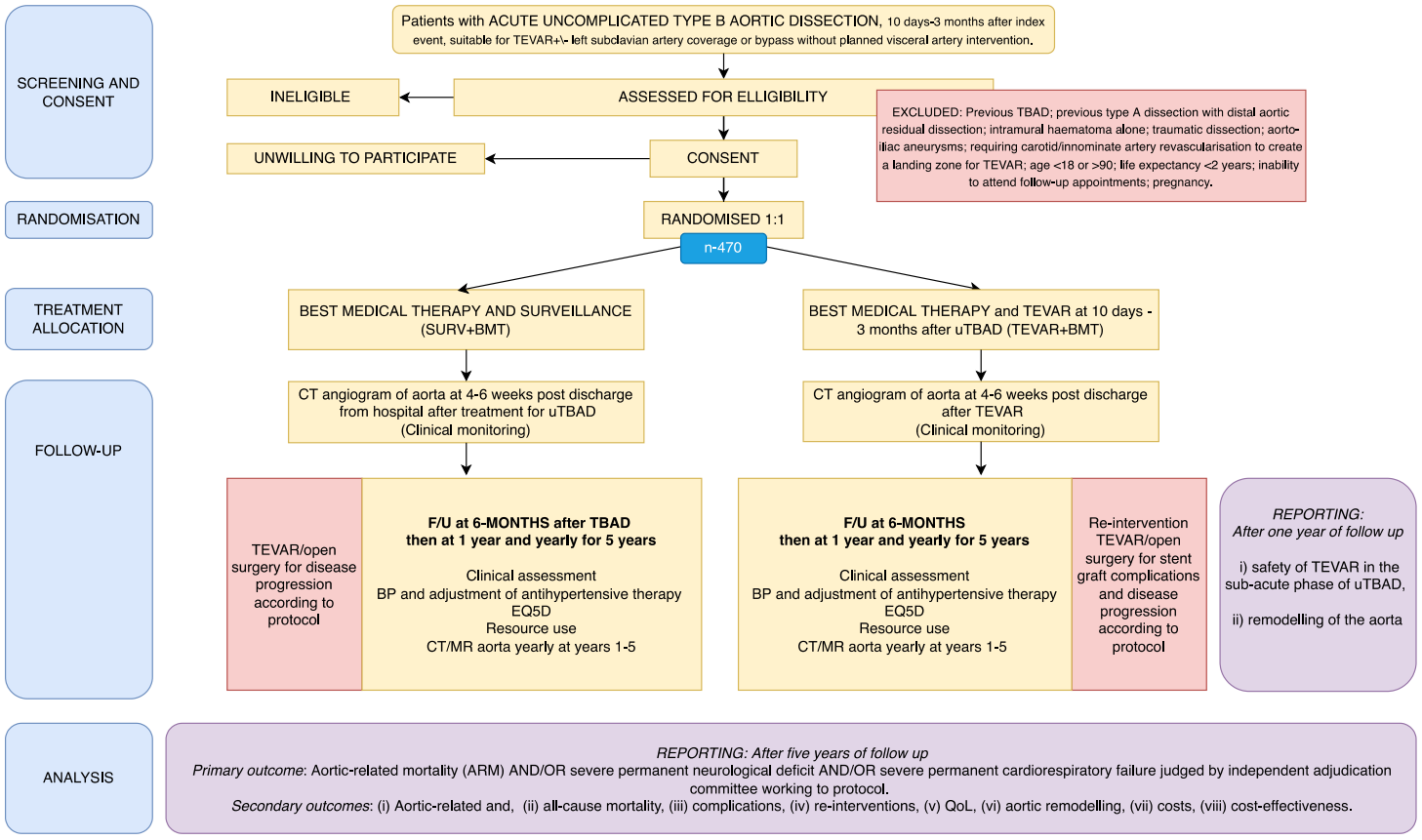
TRIAL SUMMARY

Public Title	Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST).	
Scientific Title	Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST): A randomised trial to assess the clinical and cost-effectiveness of thoracic endovascular aortic repair in the subacute phase after uncomplicated type B aortic dissection.	
Protocol Number	TBC	
Country of recruitment	25 tertiary vascular centres in the United Kingdom (England, Scotland and Wales and Northern Ireland)	
Trial participants	Adults with previously untreated Uncomplicated type B aortic dissection	
Intervention	Thoracic Endovascular Aortic Repair (TEVAR) and Best Medical Therapy and Surveillance	
Control	Best Medical Therapy and Surveillance	
Key Inclusion and Exclusion	Inclusion Criteria: (i) Patients with uTBAD, 10 days-3 months after the day of admission with acute uTBAD to hospital (the date of the index event). (ii) Age ≥18. (iii) Life expectancy ≥2 years. (iv) Discharged from high dependency/critical care and not receiving opiate analgesia or similar sedatives for at least 48 hours before enrolment. (v) Willing and able to provide written informed consent: voluntary agreement to participate in the trial following full disclosure of risks and procedures required.	Exclusion criteria: (i) Complicated TBAD (ruptured aorta, aortic dilatation >5cm or visceral/limb/spinal malperfusion, persistent pain or uncontrolled BP) (ii) Known connective tissue disorder (iii) Previous TBAD (iv) Type A dissection with distal residual dissection (v) Intramural haematoma alone (vi) Traumatic dissection (vii) Aorto-iliac aneurysm (viii) Requiring carotid/innominate artery revascularisation to create a TEVAR landing zone or planned visceral artery intervention (ix) Unable to attend follow-up appointments

		(x) Pregnancy during the period where stenting of the aorta would be necessary. (xi) Participation in any other interventional clinical trial.
Study Design	Parallel arm, multicentre, open label, superiority randomized controlled trial	
Sample size	470 patients with uTBAD, identified from 25 trial centres and regional network patient identification centres.	
Date of first enrolment	01/03/2025	
Recruitment period	18 month pilot recruitment phase and 24 month main recruitment phase	
Follow up period	Patients will be followed up for a minimum of 5 years	
	Objective	Endpoint
Primary	To determine whether early TEVAR in addition to BMT and surveillance compared to BMT and surveillance decreases the composite outcome of aortic-related mortality, severe permanent neurological deficit, or severe permanent cardiorespiratory failure over five years.	Time to the first of aortic-related mortality AND/OR severe permanent neurological deficit AND/OR severe permanent cardiorespiratory failure, with minimum follow up to 5 years.
Secondary	To determine whether early TEVAR is safe and leads to increased rates of aortic remodelling over 1-year To determine whether the early TEVAR strategy is cost-effective over 5-years; and whether this strategy has lower aortic-related mortality, fewer re-interventions/complications, and has greater quality of life (QoL) over 5-years.	Aortic-related and all-cause mortality Complications of uTBAD after/without intervention and complications of intervention Reinterventions Quality of life Aortic remodelling Stroke, paraplegia, cardiorespiratory complications Costs Cost-effectiveness Controlled blood pressure

FLOW DIAGRAM

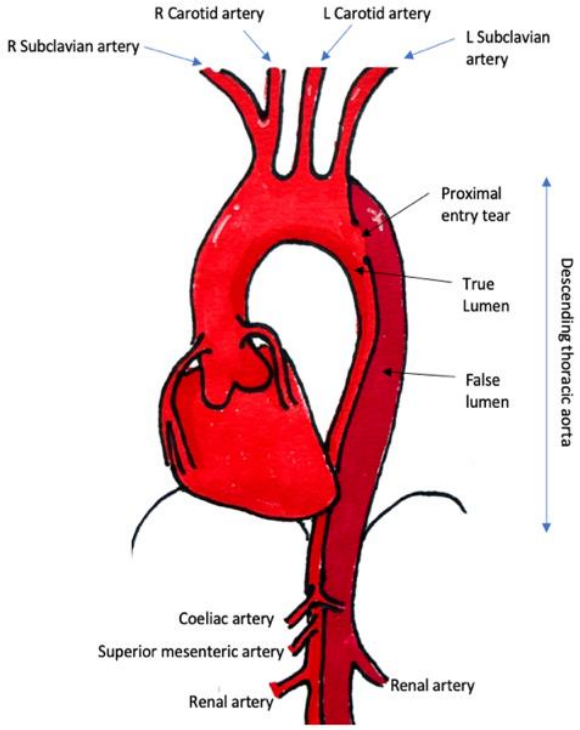
EARNEST (Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection)



1. BACKGROUND

1.1 Clinical setting

Aortic dissection is a life-threatening emergency, occurring in men and women in all age groups. UK incidence of thoracic aortic dissection is increasing along with the number of patients receiving treatment.[1] Published incidence of aortic dissection varies, between 0.5–6.3 per 100,000 person years.[2] The Well-executed Oxford Vascular Study,[3] the most relevant to this proposal estimated an incidence of 6 per 100,000 person years for all dissections with 15/52 events due to TBAD. Therefore, one may estimate that there will be 1,163 people with TBAD dissections each year in the UK, more than 60% will be uTBADs.[4]



In aortic dissection, a primary tear or defect in the intimal lining of the aorta or bleeding within the media of the aorta results in separation or dissection of the layers of the aortic wall. The dissection may progress proximally or distally. Two or more distinct channels form - the true and false lumen. Dissection entry tears distal to the left subclavian artery and dissection extending through the thoracic and often the abdominal aorta (see left figure) are classified as Stanford type B aortic dissections (TBAD). Immediate complications occur in some patients with TBAD due to a restriction of blood flow through the true lumen causing malperfusion of the end organs (e.g., gut, kidney, spine, lower limbs); direct occlusion of the branches of the aorta by the intimal flap (lamella); or from aortic dilatation and rupture of the thin, fragile wall of the false lumen. Immediate treatment is needed. TBAD patients without major complications, with uTBAD, are conventionally treated medically, with BP management and entered onto a surveillance programme. European Society of Vascular Surgery guidance supports this treatment strategy.[5]

With conservative treatment of uTBAD, approximately 1/3 of patients develop late aneurysmal change with risk of rupture. Therefore, if fit, patients with known aortic expansion are offered an operation when the aorta reaches 5.5-6cm in diameter. These procedures are usually complex, extensive operations and carry a significant risk of death. The 30-day mortality rate in the effective treatment of thoracic aortic aneurysms (ETTAA) study was 6.7% after endovascular treatment and 11.1% after open surgery for chronic aneurysms of the aorta. Major complications such as paraplegia, stroke, myocardial infarction, respiratory failure and renal failure are frequent.[6, 7] The cost to the NHS is significant. In addition, the quality of life of patients under surveillance may be significantly impaired.

1.2 Intervention details

The intervention proposed is TEVAR in the sub-acute phase after acute uTBAD.

It has been proposed that early TEVAR to close the primary entry tear will be most effective in promoting thrombosis of the false lumen during the subacute phase whilst the dissection flap retains its plasticity, thereby allowing the aorta to remodel so avoiding long-term expansion and the need for more complex, highly expensive procedures.

1.3 Rationale for the study

A review of the evidence assessing the use of TEVAR early after uTBAD reveals two RCTs involving 201 patients,[8, 9] registry studies involving nearly 2000 patients,[4, 10, 11] a propensity matched analysis of 145 patients,[12] and a systematic review with 14,706 patients,[13].

One RCT [9] involving 61 patients showed that TEVAR was safe, with no mortality or stroke. In this study, incomplete false lumen thrombosis (and hence a much higher chance of late dilatation) was found in 43% of the stenting group but 97% of the medically treated group. Forty-five percent of the medically treated group (BMT and surveillance) had aortic dilatation compared to 37% in the TEVAR and BMT group, but the study did not go on to examine long term clinical outcomes. There has been one RCT, examining clinical outcomes, allocating 140 patients to BMT and surveillance or TEVAR and BMT. This trial again showed remodelling of the aorta. The trial was extended to 5-years and using a landmark analysis strategy (designating a time point during follow-up (known as the landmark time) and analysing only those participants who have survived until this point) there was a significant advantage to stenting. This trial included patients 2-52 weeks after TBAD and so many received a stent once the aortic dissection flap between the true and false lumen lost its plasticity, so the expected remodelling of the aorta and closure of the false lumen would be less effective. Neither RCT reported cost-effectiveness.

Several registry-based publications have demonstrated an advantage to early TEVAR. A propensity matched analysis recorded that although the adverse event rate at 30-days after TEVAR was greater than in the BMT group, all-cause mortality in the TEVAR group was significantly lower at 5 years than that of the BMT group (8.1% vs. 17.8%), and aortic-related mortality was also lower in the TEVAR group compared to the BMT group (5.9% vs. 13.9%).[12] These 2 original RCTs and 4 observational studies were incorporated into one meta-analysis, involving 14,706 patients in total, of which 1,066 had TEVAR.[13] The aim was to compare peri-operative and late outcomes of patients with acute and subacute uTBAD treated by TEVAR or BMT. For the BMT group there was a lower early risk of stroke but the risk of late all-cause mortality (HR 1.54, 95% CI 1.27-1.86, $p < .001$) and aorta related mortality (HR 2.71, 95% CI 1.49-4.94, $p = .001$) was significantly higher than with TEVAR. Clearly the observational nature of the included studies means that the study suffers from inherent bias.

1.4 Risk / Benefit Assessment

At present there is no clinical consensus on the best way to treat patients with acute uTBAD. Given the risk of immediate complications with early TEVAR, and the fact that 2/3 patients do not develop aneurysms and hence will never need surgery, there is equipoise amongst clinicians as to whether early stenting of uTBAD is justified. A recent international expert survey of the management of uTBAD [14] concluded that “about half of surgeons recommended pre-emptive TEVAR [TEVAR in the sub-acute phase] in selected cases”. This was largely influenced by the surgeon’s predisposition towards intervention. In the UK there is significant variation in practice from centre to centre. A survey of 18 centres involved in this bid, showed that 50% stent a variable proportion of patients with uTBAD, but TEVAR is not undertaken in other centres that always opt for a conservative approach with BMT. Overall <10% of patients presenting with uTBAD are currently being stented in participating centres. All 25 centres in our bid agree there is sufficient uncertainty for them to have equipoise in randomising within EARNEST.

If a clear clinical advantage is shown in those receiving early TEVAR, a treatment for uTBAD patients that improves long term mortality and quality of life, may be offered. Patients that were interviewed in the preparation of this trial would welcome a definitive, proven management pathway for their condition. Many, who were treated medically with uTBAD, and had late dilatation of the aorta felt “relief when the stent was finally fitted”.

The trial cannot be achieved using registry data or National datasets. The National Vascular Registry (NVR), a clinical audit in England and Wales commissioned by the Health Quality Improvement Partnership, at present only studies procedure outcomes and does not capture long-term follow-up data, and so cannot inform whether medical treatments for dissection are more effective. Coding strategies for dissection in administrative datasets are rudimentary and do not give the extent of intervention nor effective follow-up of outcomes. The International Classification of Diseases code for aortic dissection does not distinguish between acute or chronic, or extent. The OPCS classification of interventions and procedures does not distinguish between TEVAR for acute or chronic disease. Importantly, quality of life and costs are not captured. Thus, an RCT, with adequate recruitment and long term follow up is necessary.

OBJECTIVES AND ENDPOINTS

1.5 Primary Objective

The objective of this trial is to test the hypothesis that in patients with uTBAD, TEVAR in the subacute phase, from 10 days to 3 months and BMT and SURV (TEVAR+BMT+SURV) confers a long-term advantage over BMT and surveillance (BMT+SURV), and that this practice is cost effective.

The primary aim of this trial is to determine whether a policy of TEVAR+BMT+SURV in the subacute phase, vs BMT+SURV with late aortic repair only if required, significantly decreases the composite outcome of aortic-related mortality, severe permanent neurological deficit, or severe permanent cardiorespiratory failure over five years.

1.6 Secondary Objective

Secondary aims are to: Determine the safety of TEVAR in the sub-acute phase in patients with uTBAD (i.e., to determine whether this policy is safe in the short term); measure differences in the extent of aortic remodelling at 1-year between groups; measure costs and cost-effectiveness at 5-years; record 5-year outcomes of the individual components of the composite outcome - aortic-related mortality, stroke, paraplegia, cardiorespiratory complications; compare re-intervention rates in both groups; determine quality of life (QoL) over the duration of the study.

1.7 Primary Endpoint

The Primary outcome will be time to the first of aortic-related mortality AND/OR severe permanent neurological deficit AND/OR severe permanent cardiorespiratory failure, from randomisation to a minimum follow up to 5 years, or death from any cause. A permanent event will be defined as no change in condition over 3 months and no prospect of significant improvement as assessed by PI for the site. Disability after stroke/paraplegia defined as Barthel index-severe <60 (appendix 1). Cardiac failure defined as the NYHA classification-severe (NYHA IV) (appendix 2). Respiratory failure defined as WHO Performance status-severe ≥4 (appendix 3).

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

1.8 Secondary Endpoints

Secondary outcomes include:

- Aortic-Related mortality
- All-Cause Mortality
- Complications including stroke, paraplegia and cardiorespiratory failure
- Reinterventions
- QOL
- Aortic Remodelling
- Costs
- Cost-Effectiveness
- Controlled blood pressure

1.9 Summary Table of Endpoints

	Endpoints	Timepoint(s) of evaluation of this endpoint

Primary	Time to first of aortic-related mortality AND/OR severe permanent neurological deficit AND/OR severe permanent cardiorespiratory failure	Throughout follow up from randomisation until the first composite event. Patients censored if there is a competing event (non-aortic-related death, patient withdrawal or end of the study). Reported when all patients are five years after randomisation.
Secondary	Aortic-related mortality	Throughout follow up from randomisation until the aortic-related death. Patients censored if there is a competing event (non-aortic-related death, patient withdrawal or end of the study). Reported when all patients have completed one year for the TEVAR group and five years after randomisation for all patients.
	All-cause mortality	Throughout follow up from randomisation until death from any cause. Reported when all patients have completed one year for the TEVAR group and five years after randomisation for all patients.
	Complications including stroke, paraplegia and cardiorespiratory failure.	Throughout follow up. Reported when all patients have completed one year for the TEVAR group and five years after randomisation for all patients.
	Reinterventions	Throughout follow up. Reported when all patients have completed one and five years after randomisation.
	QoL	Measured at baseline prior to group allocation, and at 6 weeks, 6 months, 12 months and then annually from randomisation until the end of follow up. QOL will be assessed using EQ-5D-5L questionnaires.
	Aortic remodelling	At one year after TEVAR in the intervention group and at five years measured using CT/MRI scans assessed using specific CT analysis protocol from core lab.

	Costs	Health resource use and costs will be measured across follow up assessments and will be analysed at 5 years
	Cost-effectiveness.	Health resource use and costs will be measured across follow up assessments and will be analysed at 5 years
	Controlled blood pressure	Blood pressure will be recorded at baseline prior to group allocation, and at 6 weeks, 6 months, 12 months and then annually from randomisation until end of follow up and analysed at 5 years.

2. STUDY DESIGN

2.1 Design

EARNEST is a multicentre, open label, superiority RCT, allocating consenting patients with uTBAD in the sub-acute phase in a 1:1 ratio to TEVAR and BMT and surveillance (TEVAR+BMT+SURV) or BMT and surveillance (BMT+SURV). It will have adjudicated endpoints and an internal pilot. Each patient will be followed up for a minimum of 5-years.

Patients with uTBAD in the sub-acute phase (from 10 days to 3 months after the aortic dissection occurs) will be identified at vascular centres and regional network hospitals. After consent, participants will be allocated in a 1:1 ratio to TEVAR and BMT (TEVAR+SURV+ BMT) or BMT and surveillance (BMT+SURV) using a using a minimisation algorithm, incorporating a random element, to ensure groups are well balanced for centre, age and sex. We refer to this as randomisation.

Those in the TEVAR+BMT+SURV group will undergo the intervention, TEVAR, at 25 specialist vascular sites in the UK. To ensure the highest standards of care and consistency across all participating centres in the clinical trial of Thoracic Endovascular Aortic Repair (TEVAR) for Type B Aortic Dissection (TBAD), a credentialing process will be implemented. This process will assess each centre's capability, infrastructure, and experience in performing TEVAR for uTBAD, ensuring compliance with established guidelines and standards.

Criteria for Credentialing for Participating Centres:

1. Multidisciplinary Team (MDT) and compliance with standard procedures:

- Centres must have an established MDT experienced in managing TBAD cases, including vascular surgeons, interventional radiologists, cardiologists, and specialist nurses.
- The MDT must demonstrate compliance with the "Provision of Vascular Services" document distributed by the Vascular Society of Great Britain and Ireland (2021).

2. Infrastructure and Facilities:

- Centres must provide comprehensive details of the unit's infrastructure and available facilities for the treatment of TBAD patients, including endovascular suites, post-operative care facilities, and availability of advanced imaging technologies.

3. Standard Operating Procedures (SOPs) and Service Provision:

- Centres must submit their SOPs and detailed documentation of their uTBAD patient care pathways, including pre-operative, intra-operative, and post-operative management protocols.

4. TEVAR Volume and Experience:

- Evidence of procedural volume must be provided, demonstrating:
    - A minimum of 40 TEVAR cases in the last 5 years or 25 cases in the last 2 years.
    - For dissection-specific TEVAR cases, a minimum of 20 cases in the last 5 years or 10 cases in the last 2 years.
- Centres must detail the experience of key operators involved in the trial, including their qualifications and volume of procedures performed.

5. Clinical and Technical Outcomes:

- Centres must provide data on clinical and technical outcomes for the last ten dissection cases treated with TEVAR, including complication rates, procedural success, and patient outcomes.

Evaluation Process:

A credentialing panel will review the submitted documentation from each centre. This panel will consist of:

- An experienced vascular surgeon, and interventional radiologist, cardiologist, a primary care clinician, a specialist nurse
- The panel will assess each centre based on the submitted evidence, focusing on their experience, safety record, and clinical outcomes. The assessment can be done virtually or on email.

Support for Developing Centres:

Centres or networks that do not fully meet the credentialing criteria will be offered training and mentoring. This will be aimed at building the necessary capacity and capability to participate in the trial. The training will include:

- Workshops and simulation-based training for key operators.
- Mentorship by experienced centres to establish appropriate care pathways and MDT practices.
- Monitoring and support during the initial phase of trial participation to ensure adherence to trial protocols and standards.

The TEVAR+BMT+SURV group will be assessed with CT/MRI at 6-weeks to ensure accurate stent placement.

All patients will receive BMT according to local practice standard of care. Physicians are directed to the European and International Guidelines for management of patients with dissection.

The BMT+SURV group will receive CT or MRI surveillance at 6-weeks post discharge for clinical monitoring as standard clinical practice in the UK. Intervention with TEVAR in the BMT+SURV group will be undertaken only if clinically indicated as per current clinical guidelines.[5]

All patients will be seen at 6-weeks, 6-months, one year and yearly (to five years after enrolment) when clinical and cost-effectiveness data will be collected. Both groups will undergo CT/MRI assessment at one year and yearly (to five years after enrolment).

2.2 INTERNAL PILOT

An 18-month internal pilot study will be conducted to ensure recruitment targets are realistic and the targets for recruitment are achievable. This will comprise three phases (site initiation and early recruitment, nested qualitative study (known as the Quintet Recruitment Study) and main internal pilot phase).

At the end of the internal pilot phase (at 18-months), the number of sites open to recruitment, recruitment rates and adherence to allocated treatments will be assessed. Red, amber and green outcomes will be set for recruitment, site opening and data completion (please see section on planned recruitment for further details.)

Quintet Recruitment Intervention (QRI) Sub-study – Qualitative research to optimise recruitment

Objectives:

The aim of the QRI is to work with EARNEST 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:

- To determine any training that needs to be developed, or feedback given to members of the clinical care team approaching and recruiting patients and ensure inclusivity.
- To determine any modifications in patient-facing materials that would improve the inclusivity of patient recruitment.

Primary outcome:

- More than half of eligible patients with uTBAD accept randomisation.

Secondary outcome.

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

Patients for this study will be recruited during the screening phase at selected sites. The Quintet Recruitment Intervention (QRI) [15, 16] will be used for semi-structured interviews (see Appendix 4 for script guide), with individuals involved in screening and presenting EARNEST to patients, will take place across all sites (n=5-10 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 4). Interviews will be conducted by the University of Leicester EARNEST trial QRI team Interviews may be carried out on the telephone or via video conferencing for some participants. They will be recorded digitally and analysed following the conventions of thematic and the constant comparison approach. Summaries of pseudo- anonymised findings will be presented to EARNEST 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.

3. PARTICIPANT ENTRY

3.1 Study setting and population

(i) Inclusion criteria

- Patients with uTBAD, 10 days-3 months after the day of admission with acute uTBAD to hospital (the date of the index event).
    - *Notes:*
        - *patients are allowed left subclavian artery coverage/bypass and/or adjunctive procedures on/to the iliac vessels to permit safe introduction of the delivery device.*
        - *Stenting must be planned to occur within 3 months after index event*
- Age ≥18.
- Life expectancy ≥2 years.
- Discharged from high dependency/critical care and not receiving opiate analgesia or similar sedatives for at least 48 hours before enrolment.
- Willing and able to provide written informed consent: voluntary agreement to participate in the trial following full disclosure of risks and procedures required.

(ii) Exclusion criteria

- Complicated TBAD (ruptured aorta, aortic dilatation >5cm or visceral/limb/spinal malperfusion, persistent pain or uncontrolled BP)
- Known connective tissue disorder
- Previous TBAD
- Type A dissection with distal residual dissection
- Intramural haematoma alone

- Traumatic dissection
- Aorto-iliac aneurysms
- Requiring carotid/innominate artery revascularisation to create a TEVAR landing zone or planned visceral artery intervention
- Unable to attend follow-up appointments
- Pregnancy during the period where stenting of the aorta would be necessary.
- Participation in any other interventional clinical trial.

There will be no patient excluded as a result of sex, geographical location, disability, gender, marriage and civil partnership status, ethnicity, religion or belief, sexual orientation, socioeconomic status or access to health or social care. There will be no exclusion of patients who suffer a uTBAD during pregnancy and maternity, although the mother cannot undergo the procedure whilst pregnant as there will be significant radiation risks to the child.

4. PROCEDURES AND MEASUREMENTS

4.1 Identification and recruitment of participants

Patients with uTBAD will be invited to take part in the trial once the requirement for intensive care or high dependency care has ended and the patient has not received opiate analgesia for at least 48 hours. Recruitment may occur in NHS hospitals in the UK when patients are:

- At the hospital before discharge
- In the outpatient setting at review after admission for uTBAD

Trial centres will be vascular hubs/centres able to deliver BMT+SURV and TEVAR+BMT+SURV arms of the study for uTBAD patients. Spoke acute NHS hospitals will be effective patient identification centres. Participants will be identified by vascular surgeons, cardiologists, cardiac surgeons, research nurses and physicians at vascular units acting as principal trial centres. There is no payment for taking part in this study. The researchers won't receive any personal payment over and above normal salary, or any other benefits or incentives.

4.2 Screening and pre-randomisation evaluations

There is no test required before the patient enters the trial. 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 (including whether complicated, uncomplicated and stented outside of trial) or for non-participation to help inform study progress.

Potential participants will be given information on the trial by local research staff when appropriate (which may be <10 days after their acute uTBAD or after discharge) and

consented at or after 10 days. Each potential participant will be given a copy of the patient information sheet (PIS) and informed consent form (ICF). potential participants will be given at least 24 hours to read the PIS and consider their participation.

The consent may only take place once the index admission requirement for intensive care or high dependency care has ended, and the patient has not received opiate analgesia for at least 48 hours. Informed consent must be obtained before any study procedures are performed. After consent, participant baseline assessments can be performed and eligibility can be confirmed. Sites will make provisions for translation during the consent process so that the process can take place in the participants native language.

4.3 Randomisation and Blinding

Randomisation: 470 participants will be allocated to treatment group (1:1) by minimisation, which assigns the next patient to the group that balances the main prognostic factors (e.g., age, sex, centre) with high probability (e.g., 75%). This will be generated by computer algorithm and released after checking patient eligibility and written consent. This will be implemented by a validated web-based system Sealed Envelope. Once a participant is confirmed to be eligible for randomisation, qualified site staff will register the participant on the system and randomise them. A participant ID will be generated which must be used to identify participants on CRFs from this point.

Blinding: For ethical and practical reasons, participants and clinicians cannot be blinded to treatment allocation. However, endpoints will be adjudicated by an expert panel (PROBE study - Prospective Randomized Open, Blinded End-point).[18]

4.4 Visit Schedule

Visit	0	1	2	3	4	5-9
	Screening	Consent	FOR TEVAR+BMT+ SURV only TEVAR Intervention	Clinical and research assessment	Clinical and research assessment	Clinical and research assessment
TIMEPOINT	Within 3 months of index uTBAD	After the requirement for intensive care or high dependency care has ended, and the patient has not received opiate analgesia for at least 48 hours and from 10 days to 3 months of	10 days-3 months after index uTBAD	FOR BMT+SURV 6 weeks after discharge from hospital admission for the index event [c] (±14 days) FOR TEVAR+BMT+ SURV	6 months after randomisation (±30 days)	1 year and yearly to 5 years after randomisation. (±30 days)

		index uTBAD, noting TEVAR must be performed in 3 months after index event		6 weeks after TEVAR [c] (±14 days)		
Inclusion & exclusion criteria	x	**x**				
Informed consent		**x**				
Demography		**x**				
Medical history		**x**		**x**	**x**	**x**
Clinical assessment		**x**		**x**	**x**	**x**
Clinical details of uTBAD admission		**x**				
Blood pressure[a]		**x**	**x**	**x**	**x**	**x**
CTA aorta		**X**		**X[b]**		**x**
Site report of CT Aorta		**X**		**X**		**x**
Transfer of CT to core lab		**X**		**X** (six weeks after discharge from hospital after index event OR six weeks after TEVAR)		**X, at 1 and 5 years only**
EQ-5D-5L		**x**		**x**, measured before imaging results are relayed to the participant	**x**, measured before imaging results are relayed to the participant	**x**, measured before imaging results are relayed to the participant
Procedural details			**x**			
Health resource use, from NHS and personal and social care				**x**	**x**	**x**
Document re-intervention				**x**	**x**	**x**
Document adverse events			**x**	**x**	**x**	**x**

[a]*Standardised BP measurement: This will be measured using standard protocols. At each visit, three BP recordings will be measured in the sitting position using a validated semi-automated device after at least ten minutes rest. The mean of the second and third readings will be used in analyses. Smoking or vaping will not be permitted for 30 minutes before BP measurement.*

[b] *If the participant has already undergone a scan at 6 weeks prior to randomization, ie. The patient has been randomised after 6 weeks from discharge, an additional clinical 6 week scan will not be required. All images should however be transferred to the core laboratory*

[c] *Participants allocated to the TEVAR+BMT+SURV group will have a clinical 6 week scan to ensure adequate stent placement.*

4.5 Follow-up

Follow up visits will take place at each of the sites in a clinical examination room for interview, examination, BP readings and required questionnaires to be completed. Each study visit will be expected to take less than one hour including rest periods for the subject.

Data will be collected on electronic case report forms using a study database called Sealed Envelope which is a regulatory-compliant database and is sponsor-approved for non-CTIMP studies.

Participants will be consented for the central study team to access routinely collected healthcare data, confirming whether the patient has had additional procedures/hospital admissions during the follow up period. Consent will also allow for identifiable data to be linked with the national databases including the National Vascular Registry data, Hospital Episode Statistics data (in England), CHI data, Electronic Data Research and Information Service DRIS (in Scotland) and from the Office of National Statistics. The identifiable fields (NHS number) required for linkage will be encrypted using a one-way encryption algorithm. We will ask patients if they are happy to give consent for their health status to be followed up over time. This will be done by linking the patient's identifiable data with records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register, or any applicable NHS information system. This will allow us to track what happens after the study finishes and observe if anyone gets further tests/investigations and treatment they may have.

As uTBAD may not develop for many years, we will also ask patients to give consent for us to keep personal data stored or accessed for 15 years on the NHSCR (National Health Service Care Register) so that data from national registries can be evaluated. For instance, long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Office for Health Improvement & Disparities

4.6 Core Lab Evaluations

Anonymised DICOM CT data will be transferred to the core lab from site electronically or via CD. CT data from baseline (the first CT scan after the index uTBAD) at six weeks after discharge from hospital (after conservative management or after TEVAR) and at one year and five years after randomisation.

Data will be analysed according to a specific core lab protocol.

Incidental findings will potentially be identified on review of CT scans in the core lab. In each case the incidental finding will be reported to the principal investigator of the site and local protocol will determine the treatment of the individual.

5. INTERVENTION

5.1 Thoracic endovascular aortic repair

The health technology being assessed is TEVAR, specifically used in participants in the subacute phase (defined as 10 days to 3 months) after uTBAD.

The aim of the stenting procedure will be to close the primary entry tear of the dissection, preventing flow into the false lumen and inducing positive remodelling of the aorta. This procedure has been shown to reduce the long-term risk of aortic dilatation (which if untreated leads to rupture) and requirement for aortic repair (see below).

Participants will undergo stenting of the aorta to close the primary entry tear with any CE marked thoracic stent device system.

All procedures should be planned on a 3D workstation as standard.

All participants must undergo anaesthetic assessment.

The procedure may be performed under general, local, or regional anaesthetic. 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 (with formal artery closure at the end).

Any reasonable adjunct/approach to provide safe access is permissible, including but not limited to adjunctive procedures such as fashioning of a conduit onto the iliac vessels to permit safe introduction of the delivery device.

When considering the landing zone of the stent the clinician must plan to: close the proximal entry tear; land the stent in healthy, non-dissected aorta; and aim for 2cm of landing zone measured from the proximal extent of the primary entry tear, however, in cases of dissection this is not a mandatory requirement if the operator is confident that a seal of the false lumen can be achieved.

In order to obtain a sufficient landing zone, the subclavian artery may be covered, with or without revascularisation with a carotid-subclavian bypass graft or standard endovascular technique to allow continued perfusion (e.g., chimney, fenestration/scallop, branch).

Single and staged procedures (as long as the aortic stenting is planned to take place between 10 days and 3 months after the presenting TBAD) will be permitted.

A maximum oversizing of approximately 10% will be recommended, with estimation of the aortic size made at the level of the left subclavian artery. For some graft types a lower oversizing is advisable. The length of the stent used will be determined by the clinical team. We recommend coverage of 20-25cm of the thoracic aorta landing in a non-angulated segment as standard. However, the extent of aortic coverage will depend on many factors (including previous aortic repair, length of dissected area, secondary tears) that may influence the rate of paraplegia, and will be at the discretion of the operator ultimately.

Ancillary treatments to close the distal re-entry tears and reduce false lumen perfusion (such as the STABILISE technique) will not be recommended as part of the clinical guidelines, but centres will be able to utilise these techniques if deemed necessary by the operator or there are significant perceived advantages to the technique.

At the end of the procedure post-stent intra-arterial digital subtraction quality control images should be obtained.

Post-operative participants receiving TEVAR must be managed in a high dependency unit setting utilising established centre specific neurological protection strategies.

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 local NHS institutions.

The procedural aspects and intervention adherence must be recorded using the TEVAR case report form.

5.2 Best medical therapy

All participants in both arms will receive BMT, which is standard of care in the UK, in an attempt to reduce the progression of aortic dilatation subsequent hospital admission rates, and the need for late dissection related aortic procedures.

Participants should receive treatment in accordance with the standard of care protocols established at each participating site. The BMT expectations will be informed by established guidelines including the European Society of Vascular Surgery guidelines, which are established practice in the UK, the 2010 American College of Cardiology and the American Heart Association “Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease”.

Treatment goals will be to reduce aortic wall stress by controlling heart rate to less than 60 beats per minute and systolic BP less than 120mmHg. Specific treatment regimens will be on a patient specific basis at the discretion of local specialist teams.

We advise that all participants should undergo 24-hour BP recording within 6-weeks of admission for uTBAD. For those with a significant atherosclerotic risk the advice will be that BMT should be maximised by the addition of a statin and antiplatelet agent. Smoking cessation will be advised

Where clinically indicated according to local protocol, participants in both trial arms will receive intervention on the aorta (either secondary interventions in the TEVAR+BMT+SURV group or primary interventions (e.g. for aneurysmal degeneration) in

the BMT+SURV group) which is standard of care in the UK according on current European Society of Vascular Surgery guidelines. In this pragmatic trial, we advise reference to the guidance provided by the European Society of Vascular Surgery [5], but the decision to treat will be at the discretion of the local clinical team.

5.3 Permanent Discontinuation of Study Intervention and Withdrawal from Study

(i) Permanent discontinuation of study intervention

Participants may not undergo the study intervention (TEVAR) for the following reasons:

- At the request of the participant.
- If the investigator considers that a participant's health will be compromised by the study intervention (TEVAR) due to Adverse Event/Serious Adverse Event or concomitant illness that develops after entering the study.

(ii) Withdrawal from Study

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

- Participant decision
- Loss to follow-up

(iii) 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.

6. SAFETY REPORTING

6.1 Adverse Event (AE)

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.

6.2 Adverse Event recording

Adverse events will be recorded at each study visit. The following will be recorded 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. SAEs will be recorded throughout the study.

In this study, there may be a number of potential common aortic related events that occur which require hospitalisation but will not be required to be reported as SAEs but must be collected as AEs within the eCRF if the adverse event either occurs within 90 days of the index TEVAR procedure or is aortic related.

The following will be noted as aortic related events:

- Any adverse event within 30 days of aortic surgery
- Access vessel dissection or rupture or pseudo-aneurysm
- Endoleak
- Proximal or distal re-entry tears
- Graft kinking (requiring re-intervention or symptomatic)
- Graft migration of >5mm
- Graft thrombosis/stenosis/occlusion
- New onset limb ischaemia including new onset claudication
- Mesenteric ischaemia/angina
- New onset renal failure/deterioration
- Paralysis/paraparesis
- Stroke
- Amputation
- Retrograde aortic dissection
- Aortic rupture/bleeding/
- Graft infection
- Re-intervention or any endovascular or open arterial procedure.

(iv)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

(v) Causality of Adverse Events

The assessment of causality will conform to the following definitions:

- Unrelated: No evidence of any causal relationship with the intervention or trial conduct
- Unlikely: There is little evidence to suggest there is a causal relationship with the intervention or trial conduct 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 with the intervention or trial conduct. 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 with the intervention or trial conduct and the influence of other factors is unlikely.
- Definite: There is clear evidence to suggest a causal relationship with the intervention or trial conduct and other possible contributing factors can be ruled out.

6.3 Serious Adverse Events (SAE)

(vi)Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

** "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.

6.4 Reporting of SAEs

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.

(vii) Related SAEs

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

(viii) Unexpected SAEs

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

(ix) 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.

Follow up of participants who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised.

6.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/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.

7. STATISTICAL ANALYSES

7.1 Sample Size and power considerations

The samples size has been calculated to be 470 participants (235 in each arm), followed up for 5 years.

Our power calculations were made after reviewing published data and re-analysis of data from the ETTAA national cohort study of patients with thoracic aortic aneurysms.[19] Primary outcome is the composite of aortic-related mortality AND/OR severe permanent neurological deficit AND/OR severe permanent cardiorespiratory failure.

Primary endpoint incidence in the SURV+BMT arm of the study: the estimated aortic-related mortality at 5 years is 14.8% taken from the combined results of one long term RCT, one high quality cohort study, and one propensity matched analysis [10, 20, 21]

Because the control group has no intervention, the estimated early (up to 30 days) severe permanent neurological deficit and/or cardiorespiratory failure is assumed to be 0% for the BMT group. These complications were not observed in either of two RCTs or a propensity matched analysis in TEVAR or BMT groups.[9, 20, 21]

Using estimates from the INSTEAD trial, [21] the 5-year risk of surgery/stenting was 26.5% in the BMT group. 78% of these patients would be suitable for a stent, with the other 22% of patients requiring surgery. These later interventions are more likely to be complicated and/or emergency procedures, with late severe permanent neurological deficit/cardiorespiratory failure estimated at 8% for those undergoing stenting and 11.29% for open procedures (based on data from ETTAA and observational data from surgical series.[7, 19] Combining risk of a late intervention, with risk of severe permanent neurological deficit/cardiorespiratory failure after an intervention, we expect non-fatal components of the primary outcome (i.e., patients who do not die within five years) of 2.31%.[1]

Adding the 14.8% of patients who die within 5 years, the early 30-day non-fatal event rate of 0%, and the longer term non-fatal serious event of 2.31%, ***the estimated 5-year incidence of the composite primary endpoint is 17.11% in the BMT group.***

Primary endpoint incidence in the TEVAR+BMT arm: The estimated aortic-related mortality at 5 years is 5.39% taken from the combined results of one long term RCT and one high quality cohort study and one propensity matched analysis [10, 20, 21] This difference in mortality between SURV+BMT and TEVAR+BMT groups would be consistent with a HR of 2.71 estimated in a meta-analysis.[13]

The estimated sub-acute phase severe permanent neurological deficit is 1.02% for TEVAR+BMT group. Severe permanent cardiorespiratory failure was not observed in either of two RCTs or a propensity matched analysis in TEVAR+BMT or SURV+BMT groups.[9, 20, 21]

From the INSTEAD trial,[21] the risk of late intervention was 16.7% for the TEVAR+BMT group. 75% of these patients that would be suitable for a stent, with the other 25% of patients requiring open surgery. Our expert panel estimated a risk of severe permanent neurological deficit/cardiorespiratory failure of 2% (stenting) and 4% (open) of patients. This was based on a substantial decrease in the need for complex procedures in patients with previous intervention and a substantially decreased risk of emergency intervention, compared to control patients.[21] Combining risk of a late intervention, with risk of severe permanent neurological deficit/cardiorespiratory failure after an intervention, we expect non-fatal components of the primary outcome of 0.42%.[2]

Adding the 5.39% of patients who die within 5-years to the 1.02% who survive a sub-acute phase event and 0.42% who survive without a sub-acute phase event but have a serious event longer term, ***the estimated 5-year incidence of the composite primary endpoint is 6.83% in the TEVAR+BMT group.***

Thus, if there is no crossover or loss to follow up, primary outcomes are expected in 17.11 patients in the SURV+BMT arm and 6.83 in the TEVAR+BMT arm.

[1] 26.5% x 0.78 x 0.08 + 26.5% x 0.22 x 0.1129 = 2.31%
[2] 16.7% x 0.75 x 0.02 + 16.7% x 0.25 x 0.04 = 0.42%

Overall: Assuming 2.5% cross-over from each arm (low estimated because TEVAR in the sub-acute phase can only occur between 10 days and 3-months), we would expect event rates of 16.85% (=17.11x0.975 + 6.83x0.025) in the TEVAR+BMT arm and 7.09% (=6.83x0.975 + 17.11x0.025) in the SURV+BMT arm. This corresponds to an average observed event rate over the two arms of 11.97% and a hazard ratio of approximately 0.4 for TEVAR+BMT, relative to SURV+BMT (estimated from hazards based on exponential time to event rates).

Using Stata v17.0 and command, (power cox, hratio(0.4) failprob(0.1197) effect(hratio) power(0.9)), for 90% power, and two-sided type-1 error 5%, we would require 51 events in 419 patients. Inflating this to allow 10% of patients to be lost to follow up (and censored at last visit in the primary analysis), we require 57 events in 470 patients (235 in each arm), followed up for 5 years (based on Cox regression for primary analysis). The estimand for our primary analysis is the hazard ratio for the comparison between TEVAR+BMT and SURV+BMT (see the separate Statistical Analysis Plan for full details of the methods for estimating the sample size).

7.2 Planned recruitment rate

We estimate a single centre to open for the first 4 months, then recruit one centre a month until there are 25 (over 28 months). When open, the average recruitment per centre per month will be 0.7 participants.

At 18 months we expect 15 centres open, and 86 participants randomised. At the end of the internal pilot phase (at 18-months), the number of sites open to recruitment, recruitment rates and adherence to allocated treatments will be assessed

Red, amber and green outcomes will be set for recruitment, site opening and data completion. The outcome will be judged as RED if centres have recruited less than 30 participants which equates to less than 35% of the projected numbers at this stage; AMBER if centres have recruited 30-85 participants which equate to 35- 100% of the projected numbers at this stage; and GREEN if centres have recruited over 86 participants which equate to >100% of the projected numbers at this stage. At the end of the internal pilot the number of centres actively recruiting; data completion and visit completion at 6-weeks will be assessed in the same way.

Progression Criteria	Red	Amber	Green
Number recruited	<30 participants	30-86 participants	>86 participants
Number of sites opened	<5	5-15	>15
Data completion	<70%	70-85%	>85%
6-week clinical follow up completed	<70%	70-85%	>85%

Table 1: Progression criteria after 18 months of recruitment to the EARNEST trial generated using the internal pilot.

Predicted recruitment is 470 participants in the UK over 42-months, an average of 135 patients/year (we estimate this will be 1 in 4 patients with acute uTBAD presenting to sites).

7.3 Statistical Analysis

Statistical analysis is the responsibility of Prof Linda Sharples at LSHTM. The analysis and reporting will conform to the standards set by the Consolidated Standards of Reporting Trials statement.[22] Analysis will be undertaken guided by a pre-specified Statistical Analysis Plan (SAP), which will be approved by the TSC , prior to database lock. Any deviations from the SAP will be justified and documented in the final report.

(i) Analysis populations

Primary statistical analysis will be based on the intention to treat principle. Participants will remain in the study from randomisation to end of follow up and be analysed in the group to which they were randomised. This primary analysis will take place when all participants are at least 5 years post-randomisation.

An interim analysis will take place at one year after randomisation to report the outcomes of the TEVAR procedure (complication rates and early outcomes). There will be no formal assessment of the need to stop the trial on the basis of efficacy at this stage. No other interim analyses for efficacy will be undertaken.

(i) Primary Endpoint Analysis

An independent outcome adjudication committee working to strict protocols will review all reported primary endpoints using source data.

Times from randomisation to the first primary outcome component will be summarised using Kaplan-Meier estimates. Participants who do not have an event or are lost to follow up (including due to intercurrent events such as non-aortic death) will be censored at last visit. This has been termed the Hypothetical Strategy estimand, since it assumes that people who are censored would have had the same risk as those who are not censored, if they had remained in the study. The estimand for our primary analysis is the hazard ratio for the comparison between TEVAR and BMT, estimated from a Cox proportional hazards model (after checking the model assumptions) adjusting for minimisation variables age and sex as fixed effects and centres as random intercepts. The treatment hazard ratio, 95% confidence interval and Wald p-value will be reported.

(ii) Secondary Endpoints Analysis

- Similar survival model methods will be used for secondary time to event outcomes, including aortic-related mortality, all-cause mortality and reinterventions.
- The number of complications each participant experiences will be analysed using negative binomial models, with patient as the random effect, treatment arm and the minimisation factors as fixed effects and adjusting for time at risk.
- Rate of aortic remodelling between TEVAR+BMT+SURV and BMT+SURV groups will be analysed by the core lab. CT angiograms at presentation of the index event, six weeks post TEVAR/or after dissection and one year will be analysed by the core lab according to a standard protocol. The rate of false lumen thrombosis and

maximum diameter/area of false lumen, true lumen and whole aorta as well as ratios will be compared between groups.

- Patient reported outcomes measured over time, including the index value from the EQ-5D-5L, will be analysed using linear mixed models. We will first decide on the most appropriate covariance structure. This means starting with a saturated mean model (including treatment, age, sex, baseline index value and all interactions) and exploring patient-specific random intercepts, random slopes and their correlations. After fixing this covariance structure, we force treatment, age and sex into the model, assuming a constant treatment effect over time. This again reflects a hypothetical strategy estimand for the treatment effects at each time point.

(iii) Safety

All Serious adverse events will be reported by treatment arm, stratified by severity, relationship to treatment/trial conduct whether or not they are expected. Statistical monitoring of safety data by ICTU will be conducted throughout the trial and reported at agreed intervals to the DMEC.

(iv) Exploratory analysis

- We will explore the relationship between initial aortic diameter and changes over time through estimation of the correlation between random intercepts and random slopes (covariance structure).
- We will explore the effects of other baseline measurements and CT criteria and their interactions with treatment arm, on long-term aortic growth.
- Further exploratory analysis may be undertaken should it be warranted.

(v) Sensitivity Analysis

For technical details of the following sensitivity analysis, see the SAP.

- In addition to the above ITT analysis, a per-protocol population (PP) will also be defined, which will include all eligible randomised participants according to the treatment received but will exclude major protocol violations. Results from both the ITT and the PP analyses will be presented.
- In an RCT, we do not expect substantial amounts of missing baseline measurements. Therefore, the primary analysis will include complete cases only. However, analysis of the primary outcome and key secondary outcomes could be repeated after using Chained Equations to impute missing baselines multiple times, with resulting estimates of the treatment effects combined using Rubin's rules. This method will be used if more than 10% of cases have some missing baseline data. The method assumes that the incomplete baselines are *Missing at Random* conditional on measurements that are observed, an untestable assumption.
- The primary outcome analysis assumed non-informative censoring for those participants who did not have the primary outcome during follow up. We will repeat the analysis using inverse probability of censoring weights to adjust for differences between fully observed and censored survival times.

- We will consider sub-distribution hazard ratios for the primary outcome to adjust for competing risks such as death from non-aortic causes.
- Other sensitivity analyses will be completed should the trial data or analysis be deficient in another way.

(vi) Cost effectiveness

Cost-utility analysis will consider NHS and personal social services (PSS) costs including productivity losses due to sick leave. The outcomes will be presented as incremental cost per Quality Adjusted Life Year (QALY) gained.

8. REGULATORY, ETHICAL AND LEGAL ISSUES

8.1 Declaration 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.

8.2 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).

8.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the enrolment of participants, the REC 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.

(ii) 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.

Please Note: Amendments must be submitted to the Funder for review prior to REC submission.

(iii) 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.

8.4 HRA approval

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.

8.5 Other Required Approvals

Investigators must ensure that all procedures that take place as part of the trial (either early TEVAR in the subacute phase or late interventions due to complications) are compliant with the 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.

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.

8.6 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF 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 UK 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.

8.7 Insurance and Indemnity and Sponsor

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

8.8 Trial Registration

The study will be registered on a trial database (ISRCTN) in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

8.9 Informed Consent

The consent may only take place once the requirement for intensive care or high dependency care has ended, and the patient has not received opiate analgesia for at least 48 hours.

Consent may be undertaken from 10 days to three months (allowing time for TEVAR to take place if necessary) from the index event.

It will be the investigator's responsibility to obtain written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are commenced.

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.

Consent will be obtained for the central study team to access routinely collected healthcare data to confirm whether additional procedures/hospital admissions took place during the follow up period and to obtain long term health outcomes after the study has finished.

The Informed Consent Form will be signed and personally dated by both the subject and the investigator, or a person delegated to do so by the investigator. The subject will be provided with a copy of the signed Subject Information Sheet/Informed Consent Form document. The original Informed Consent Form will be retained with the source documents.

8.10 Contact with General Practitioner

It is the investigator's responsibility to inform the participant's General 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.

8.11 Monitoring, Audits and Inspections

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

8.12 Data Protection and Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the CRF 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 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.

The site investigator will preserve the confidentiality of all participants taking part in the trial, which will be conducted in accordance with the General Data Protection Regulation (GDPR).

Imperial College London is the Sponsor for this study based in the United Kingdom. The Sponsor will be using information from participants and their medical records in order to undertake this study and will act as the data controller for this study. This means that the Sponsor is responsible for looking after participant information and using it properly. Imperial College London will keep unidentifiable information about participants for 10 years after the study has finished.

Participants' rights to access, change or move their information are limited, as information needs to be managed in specific ways in order for the research to be reliable and accurate. If participants withdraw from the study, the information about them already obtained will be kept. To safeguard participant rights, the minimum personally-identifiable information possible will be used.

When participants agree to take part in a research study, the information about their health and care may be provided to researchers running other research studies in the organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country. Their information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

8.13 End of Trial

The end of the trial for safety reporting and regulatory purposes will be the database lock. This is not the Last Participant Last Visit to allow accurate recording of all clinical information and AEs/SAEs.

8.14 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.

9. DATA MANAGEMENT

9.1 Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained at participating sites to allow reliable verification and validation of the trial data. What constitutes source data for this trial will be outlined in the trial Monitoring Plan.

9.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible.

9.3 Database

We will use the SealedEnvelope database application for electronic data capture (EDC) to record case report form data for patients participating in the study (www.imperial.ac.uk/joint-research-compliance-office/project-planning/nhs-project-planning/electronic-data-capture-non-ctimps/). SealedEnvelope is a regulatory compliant database and is sponsor approved for non-CTIMP studies such as this proposal. Study staff at each participating site will enter baseline and follow up data into the online database. The database is password protected and users will have passwords to access, enter and use the data for the full study duration. All members of the research team will receive training appropriate to their role and duties and will respect and comply with patient confidentiality.

9.4 Data Collection

Details of procedures for CRF/eCRF completion will be provided in a study manual.

9.5 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.

10. STUDY MANAGEMENT STRUCTURE

The trial will be managed by the United Kingdom Clinical Research Collaboration (UKCRC) registered Imperial Clinical Trials Unit (ICTU).

The following groups and trial committees will be established:

10.1 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened and a minimum quoracy for any meeting to conduct business is 67% (two thirds) of the appointed membership. Independent members must make up a minimum of 75% of the TSC membership.

Membership should comprise an Independent Chair (holding a substantive UK based appointment), 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 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 Funder (NIHR) 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).

10.2 Trial Management Group (TMG)

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician, trial manager and two lay representatives. 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.

10.3 Data Monitoring and Ethics Committee (DMEC)

Membership of the 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 DMC charter for further details (See CR014).

10.4 End Points Adjudication Committee (EAC)

An independent Endpoints Adjudication Committee will be convened at the start of the trial, The EAC is blinded to the treatment allocation and centrally reviews and classifies suspected outcome events, verifying whether they meet protocol definitions.

Definitions of study endpoints: see section 1.9

10.5 Early Discontinuation of the Study

In case of early discontinuation of the study, the Follow-up Visit assessment should be performed for each subject, as far as possible. The statistical criteria for termination of the study will be determined by the DMEC and detailed in the statistical analysis plan (SAP).

10.6 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 Study 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.

10.7 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.

10.8 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by the Sponsor and/or QA representative of the 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 the NHS Research Governance Framework for Health and Social Care (2nd Edition).

10.9 Peer review

The peer review conducted for the study has been through the funder NIHR HTA.

10.10 Patient and Public Involvement

Patient, family, and carer involvement (PPI) has been integral to the development of the application and woven through all stages.

Two of the James Lind Alliance priority setting partnerships have identified general questions such as, “How do surgeons decide which treatment is best for aneurysms and are these decisions based on the latest evidence available?” and more specifically “What are the best ways to prevent, diagnose and treat patients with acute aortic dissection (including long-term management)?” as key questions. [https://www.jla.nihr.ac.uk/priority-setting-partnerships/vascular-conditions/aortic-top-10-priorities.htm]

In the co-design process of the trial application, we have given a written introduction to the trial in lay language to all PPI participants. We have interviewed 25 patients, relatives and carers from different age ranges and ethnic backgrounds and run a final focus group to discuss the usefulness of the trial, how to ensure good recruitment, and consent issues as well as the choice of outcome measures.

The trial was unanimously supported by all patients and carers that we interviewed. It was seen as an important research question. All interviewees and 6/7 in our final focus group would have entered into the trial themselves or advised a relative to go into the trial after an uTBAD. Our patients thought that no matter which arm the subject was enrolled into, the “enhanced level of supervision” was attractive.

Vital advice from our PPI group has been taken regarding recruitment and consent. Participants described fears about considering the trial and being consented whilst in High Dependency areas such as Intensive Care or when receiving pain medication after the acute event. Opiate analgesia can cause drowsiness, and it would be unethical to approach patients in this state. We have therefore co-designed the consent process so that patients are only approached when stable, on the ward, and not receiving opiate analgesia for at least 48 hours.

The PPI group has been instrumental in helping us decide the primary and secondary outcomes in the trial. The group discussed at length the most appropriate endpoint. They reached the conclusion that we should include all events that were life changing, led to a loss of independence, which could not be reversed, and effects that left a participant unable to adapt to have a good quality of life. For example, being “unable to walk or talk”. Participants discussed important complications that occur in discussions with clinicians and a strict definition of the end point was agreed.

The PPI group has given initial feedback regarding strategies to ensure participants do not drop out of the trial such as joint clinician and patient update meetings or webinars, written information, virtual community groups and with celebrity engagement (already engaged with The Aortic Dissection Charitable Trust). These will be developed alongside the planned qualitative research.

Regarding underserved groups, the advice from our PPI group has been to make written literature and video information in languages apart from English and to directly contact representative groups. We will translate information into three languages apart from English. In

order to make sure that women and black patients with TBAD are fairly served we will work with relevant communities/action groups.

The Trial Management Group (TMG) will involve two lay members to advise on the management of the trial: Catherine Fowler, a trustee from the Aortic Dissection Charitable Trust and relative of a patient affected by aortic dissection and a further PPI representative; Richard Bonella, a patient with a dissection on medical therapy.

The lay members will have an advisory and oversight role throughout the duration of the study and be involved in all key decisions. They will be included in decisions regarding the internal pilot and enacting of the stop/go criteria. They will be included in discussions regarding information received regarding serious adverse events and communication from the Data Monitoring and Safety Board.

Lay members on the TMG will communicate with a diverse group of 8 members of a PPI board who will meet face to face in years 1, 6 and 9 and online for the rest of the project. The panel members will meet three times per year for the first three years and then once per year thereafter until the final six months where they will again meet three times to advise on the final outputs and dissemination. These members will be selected to be a diverse and engaged group to supply opinion on the design of the trial as well as comment on information for dissemination, results of the trial and the final outputs.

We will develop trial specific and general training modules that can be attended live or watched on line for all PPI participants. We will ensure that all the PPI group have had the opportunity to be involved in training, understand the research, and understand how they can be vital to the trial design, implementation and dissemination.

The PPI board will be vital in working out strategies for recruitment and retention of participants. The members will be involved in understanding and acting on the results of the qualitative analysis of recruitment and retention in the internal pilot.

The PPI will be coordinated by a dedicated PPI administrator (band 6, 10% time) and supported by the NIHR Imperial Biomedical Research Centre's PPI team.

10.11 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 also provide an internal report to inform Imperial College of the findings.

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 The Aortic Dissection Charitable Trust) 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. We will hold a webinar for patients and carers to disseminate the results. Additionally, short, plain-English updates will be shared via social media. A yearly trial updates newsletter will be available online. The findings will also be discussed during consultations at yearly intervals, with one-to-one summaries of trial progress provided. 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 will 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 NIHR).

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

We will publish the protocol and have it available on our institutional website. This publication will be in line with ICMJE requirements and therefore explicitly state our conditions on: data types; additional available documentation; window of availability [dates indicating opening and closure of access]; eligibility of requests; types of analysis permitted; method of access. We will post the data sharing opportunity on our university websites. We will also take

queries from interested third parties to assist and guide them to the opportunity. All subsequent publications of primary and secondary outcomes will be compliant with the NIHR Open Access Policy (www.nihr.ac.uk/documents/nihr-open-access-policy/12251).

During the period of funding, our datasets will be collected and completed in the manner described above. We anticipate opening up access beyond the existing research group within 24-months after funding is complete. There will be a lock-out period to enable the key outcomes of the studies to report first after which data access will be through application to the study group. All participants will provide written informed consent for involvement in this study and permission for use of their data in scientific research (including sharing with the wider research community). We will ensure they have read and have a readily available copy of the latest version of our sponsor-approved privacy notice at the time of reading the patient information sheet and before providing consent. All external users will be bound by a data sharing agreement. This will be drawn up and ratified by Imperial Research Contracts Office and form part of the contract with NIHR (www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253). Colin Bicknell will act as the data custodian on behalf of Imperial College London and hold overall responsibility for data management. The persons responsible for data security and quality assurance will be Colin Bicknell and Linda Sharples.

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12. REVISION HISTORY

Version	Date	Summary of changes
0.1	16/07/2023	First version
0.2	24/09/2024	Second version

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: Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST): A randomised trial to assess the clinical and cost-effectiveness of thoracic endovascular aortic repair in the subacute phase after uncomplicated type B aortic dissection.

Protocol Number: Protocol Number 1.0

Signed: DocuSigned by: Colin Bicknell, BA7CA2D9B5AF40A...

Professor Colin Bicknell

Professor of Vascular Surgery

Date: 2/15/2025

SIGNATURE PAGE 2 (SPONSOR)

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

Study Title: Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST): A randomised trial to assess the clinical and cost-effectiveness of thoracic endovascular aortic repair in the subacute phase after uncomplicated type B aortic dissection.

Protocol Number: Protocol Number 1.0

Signed: Signed by: Cheuk Fung Wong EA50B2978BE7474...

Mr Cheuk-Fung Wong

Title: Research Governance Manager

Sponsor name: Imperial College London

Date: 2/14/2025

SIGNATURE PAGE 3 (STATISTICIAN)

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

Study Title: Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST): A randomised trial to assess the clinical and cost-effectiveness of thoracic endovascular aortic repair in the subacute phase after uncomplicated type B aortic dissection.

Protocol Number: Protocol Number 1.0

Signed: Signed by: Linda Sharples 632905CA455C474...

Professor Linda Sharples

Title: Senior Statistician

London School of Hygiene and Tropical Medicine

Date: 2/16/2025

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: Early Aortic Repair in patients Needing Endovascular/open Surgery for Type B Aortic Dissection (EARNEST): A randomised trial to assess the clinical and cost-effectiveness of thoracic endovascular aortic repair in the subacute phase after uncomplicated type B aortic dissection.

Protocol Number: Protocol Number 1.0

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES

Appendices are additional information to the protocol and consist of:

APPENDIX 1

Barthel Index for Activities of Daily Living (ADL)

APPENDIX 2

Cardiac failure defined as the NYHA classification

APPENDIX 3

The WHO performance status

APPENDIX 4

Quintet Recruitment Intervention Study for EARNEST trial. Script guide for semi-structured interviews

Appendix 1: Barthel Index for Activities of Daily Living (ADL)

The Barthel index will be used for grading of severity of stroke and is used in everyday clinical practice. The index scoring system and definitions for each of the scores is detailed in: MAHONEY FI, BARTHEL DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. Md State Med J. 1965 Feb;14:61-5.

Refer to table 1 for Barthel Index for Activities of Daily Living (ADL)

	+15	+10	+5	+0
Feeding		Independent	Needs help	Unable
Bathing			Independent	Unable
Grooming			Independent	Unable
Dressing		Independent	Needs help	Unable
Bowel control		Continent	Occasional accident	Incontinent (or needs enemas)
Bladder control		Continent	Occasional accident	Incontinent (catheterized, unable to manage alone)
Toilet use		Independent	Needs help	Unable
Transfers (bed to chair and back)	Independent	Needs minor help (verbal or physical)	Needs major help (1-2 people, physical) can sit	Unable
Mobility on level surfaces	Independent (but may use any aid) >50 yards	Walks with help of one person (verbal or physical) >50 yards	Wheelchair independent including corners, >50 yards	Immobile or <50 yards
Stairs		Independent	Needs help (verbal, physical, carrying aid)	unable

Total score: _____

Appendix 2: Cardiac failure defined as the NYHA classification

Along with the American College of Cardiology, the American Heart Association has identified stages of heart failure. This is known as the NYHA classification. The NYHA classification is ubiquitously used in clinical practice.

For detailed explanations on its use, researchers are directed to:

https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

Refer to table 2 for Cardiac failure defined as the NYHA classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or shortness of breath.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or chest pain.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or chest pain.
IV	Symptoms of heart failure at rest. Any physical activity causes further discomfort.

Appendix 3: The WHO performance status

The performance status is used in clinical trials as a global assessment of performance status.

Participants will be reviewed using the WHO performance status as outlined below.

0: able to carry out all normal activity without restriction

1: restricted in strenuous activity but ambulatory and able to carry out light work

2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours

3: symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden

4: completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Appendix 4: Quintet Recruitment Intervention Study for EARNEST trial. Script guide for semi-structured interviews

A. For recruiting staff

Background

1. Can you describe your current position and role in the study?
2. Do you have prior experience of working in RCTs?
3. Could you explain what the EARNEST study is about?
4. Do you think there is a need for this trial or not?
5. Could you tell me how and why you got involved in EARNEST?
6. Are you aware of any prior evidence relating to this area of research?

EARNEST recruitment pathway in site

7. Can you talk me through what happens from the time a patient is referred to your centre to the time a decision is made about whether or not they participate in the trial?

Eligibility criteria

8. Could you describe the eligibility criteria to me? *Probe for thoughts on the criteria teasing out any areas of concern they may have*

Introducing/explaining the trial

9. How do you introduce/explain the EARNEST study to patients? *Probe around randomisation, uncertainty and description of treatments, and patient responses/understanding*

Reasons for declining participation

10. Why do patients decline to participate in this trial? *Probe reasons behind decline and how recruiters respond to this*

Main recruitment barriers in EARNEST

11. How do you think recruitment is going so far?
12. What would you say are the main difficulties you face as a recruiter?
13. Can you describe specific examples of 'good' and 'less good' recruitment experiences?
14. Do you feel recruitment is well organised or could be better?
15. Do you feel there are difficulties with any particular arm?

Improving recruitment

16. What might, in your opinion, improve recruitment?

B For patients who declined randomisation

1. What did you understand about the EARNEST study?
2. How were you asked to take part in the EARNEST study?
3. What was that like?
    a. *Prompt: Who spoke to you? What were you told? Where were you at the time?*
4. What were your expectations?
5. Why did you decide to not take part?
6. Would anything have made it easier to take part?
7. Is there anything else that you think is important for me to know?
8. Is there anything else you would like to talk about?

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