BHF PROTECT-TAVI Protocol
Version 6 29/07/2024

Funder: British Heart Foundation and Boston Scientific

Sponsor: University of Oxford

Trial Management: London School of Hygiene & Tropical Medicine Clinical Trials Unit

Trial Title: British Heart Foundation Randomised Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation

Internal Reference Number / Short title: BHF PROTECT TAVI

Ethics Ref: 20/WA/0121

IRAS Project ID: 276396

Date and Version No: Version 6.0, 29/07/2024

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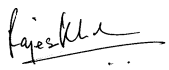
1. Contents

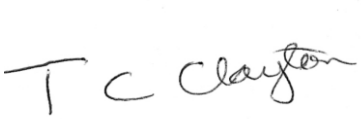
Chief Investigator Declaration

I have no competing interests to declare.

Name: Professor Rajesh Kharbanda	**Signature:** 	**Date:** 29/07/2024

Trial Statistician Declaration

I have no competing interests to declare.

Name: Professor Tim Clayton	**Signature:** 	**Date:** 29/07/2024

2. KEY TRIAL CONTACTS

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3. LAY SUMMARY

Aortic stenosis (AS) is a common life-threatening condition, where blood flow out of the heart is restricted by narrowing of the aortic valve. There are two ways to treat AS. Transcatheter Aortic Valve Implantation (TAVI) inserts a new valve inside the existing diseased valve. Surgical aortic valve replacement (AVR) involves surgery on the heart to replace the diseased valve.

TAVI is less invasive than surgical AVR. However, there are still risks with TAVI, including stroke and death, although these are lower than the risks associated with surgical AVR. Stroke in TAVI can be caused by debris released into the bloodstream by the procedure. Devices, called cerebral embolic protection (CEP), have been developed to capture some of this debris. The device is composed of filters which are temporarily placed in the arteries supplying blood to the brain. However, we do not know if the risk of stroke in TAVIs is lower with CEP or without CEP. This trial will allow us to answer this question.

In this study we will randomly assign patients having a TAVI to receive CEP during TAVI or to the current standard of care without CEP. Potential participants will be approached prior to their TAVI procedure to discuss the trial. If they are happy to take part, full informed consent will be sought. Following the TAVI, we will assess whether participants have a stroke in the following 72 hours. We will also assess other ways the CEP treatment impacts on the NHS as well following-up participants for 12 months to assess their long-term outcomes. We will recruit 9712 participants across the UK over 5 years.

4. SYNOPSIS

Trial Title	British Heart Foundation Randomised Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation
Internal ref. no. (or short title)	BHF PROTECT-TAVI
Trial registration	ISRCTN16665769
Clinical Phase	Phase III
Trial Design	A prospective open-label, outcome adjudicated, multicentre randomised controlled trial (RCT) evaluating the use of a cerebral embolic protection device in participants with aortic valve stenosis planned for treatment by Transcatheter Aortic Valve Implantation (TAVI). Participants will be randomised 1:1 into a treatment group using the cerebral embolic protection device or a control group with no cerebral protection. The primary outcome measure is stroke at 72-hours post-TAVI or hospital discharge (if sooner).
Trial Participants	Subjects with aortic stenosis planned for treatment by a TAVI.
Intervention	The intervention group will have TAVI performed with CEP. The Claret Sentinel dual-filter device (Boston Scientific, MA, USA) is a single use, embolic protection catheter inserted into the right radial or brachial artery. This is the only device currently approved for clinical use in both Europe and the USA. The device employs two filters (nitinol frames with 140-micron pores polyurethane film), one delivered to the brachiocephalic artery (Proximal Filter), and one to the left common carotid artery (Distal Filter) before TAVI. Following the TAVI procedure the system is removed.
Comparator	The comparator (control) group will have TAVI performed without the use of a CEP device (standard of care).
Primary Outcome	The incidence of stroke at 72 hours post-TAVI, or hospital discharge (if sooner)

Secondary Outcome	• Combined incidence of all-cause mortality or non-fatal stroke at 72 hours post-TAVI, or hospital discharge (if sooner) • Combined incidence of all-cause mortality, non-fatal stroke or transient ischaemic attack at 72 hours post-TAVI or hospital discharge (if sooner) • Incidence of all-cause mortality at 72 hours post-TAVI or hospital discharge (if sooner) • Win ratio for all-cause mortality, disabling stroke and non-disabling stroke at 72 hours post-TAVI, or hospital discharge (if sooner) • Incidence of all-cause mortality at 12 months post-TAVI • Incidence of all-cause mortality up to the end of the trial. This will use trial data up to 12 months, and centrally held NHS data from 12 months to the end of the trial • Incidence of stroke as defined by centrally held NHS data (described in section 14.7) between 72 hours post-TAVI or hospital discharge (if sooner) and 30-days post-TAVI • Incidence of stroke as defined by centrally held NHS data (described in section 14.7) between 30-days post-TAVI and the end of the trial • Stroke severity assessment in participants who have had a stroke within 72-hours post-TAVI or hospital discharge (if sooner) • Disability Outcome assessed up to 12 months post-TAVI in participants who have had a stroke within 72-hours post-TAVI or hospital discharge (if sooner) • Cognitive Outcome assessed up to 12 months post-TAVI (collection of cognitive outcome data now discontinued; see section 7.2) • Vascular access site related complications at 72-hours post-TAVI or hospital discharge (if sooner) and between 6-8 weeks post-TAVI • Cost-effectiveness analysis at 12 months post-TAVI
Sample Size	9712
Planned Trial Period	Planned start date: **01 August 2020** Planned end date: **31 August 2027** Total project duration: **85 months** Individual participant involvement: **12 months after TAVI procedure**
Planned Recruitment period	58 months

5. ABBREVIATIONS

AE	Adverse event
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
CEP	Cerebral Embolic Protection
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICH GCP	International Conference on Harmonisation Good Clinical Practice
LSHTM CTU	London School of Hygiene and Tropical Medicine Clinical Trials Unit
MHRA	Medicines and Healthcare products Regulatory Agency
MoCA	Montreal Cognitive Assessment
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Score
PI	Principal Investigator
QVSFS	Questionnaire to Verify Stroke Free Status
REC	Research Ethics Committee
SAE	Serious Adverse Event
smRSq	simple modified Rankin Scale questionnaire
SOP	Standard Operating Procedure
TAVI	Transcatheter Aortic Valve Implantation
TIA	Transient Ischaemic Attack

6. BACKGROUND AND RATIONALE

6.1. Background

Aortic stenosis (AS) is a common condition where the valve leading out from the heart (aortic valve) becomes narrowed (stenosed). This causes symptoms such as chest pain, breathlessness and exertional syncope and increases the risk of death. The number of patients with AS is rising as it affects the elderly, who represent an increasing proportion of the population. Treatment of AS can be by Transcatheter Aortic Valve Implantation (TAVI) or surgical aortic valve replacement.

TAVI has become an important treatment option for patients with AS who are at high-risk from surgery, and the evidence supporting its safety and effectiveness in other patient groups is increasing. TAVI is less invasive, leads to faster recovery and is associated with less morbidity than surgical aortic valve replacement. The risks of TAVI include complications from damage to the artery used for the procedure, stroke and death. However, it is likely that TAVI will be used in a wider group of patients as we gain further evidence[1,2].

Stroke is an important, but unpredictable complication associated with TAVI, and will become an even more important concern to patients and healthcare funders as TAVI is used for younger patients at lower risk from surgery, and in greater numbers as the proportion of older people increases in the population. Indeed, TAVI patients report that maintaining independence is a more important treatment goal than preventing death[3], and other studies show that stroke may be regarded as a worse health-state than death by patients[4]. The majority of TAVI related strokes are ischaemic in nature, presumed due to embolism, and occur early after TAVI [5] [6]. This suggests they are caused by debris being released into the circulation and reaching the blood supply to the brain (embolism). TAVI-associated stroke leads to prolonged hospital stay, a reduced chance of returning to independence, and a near 6-fold increased risk of death within 30 days [7] [8-10]. Stroke increases the cost of the index hospitalisation and doubles rehospitalisation costs [11]. Reducing the risk of stroke during TAVI has important implications for improving patient outcomes and decreasing healthcare resources.

6.2. Evidence for CEP in TAVI:

The evidence supporting the use of CEP in TAVI is based on three lines of investigation (i) proof-of-principle studies have confirmed that debris is retrieved from the majority of CEP devices when they are examined after TAVI [12], suggesting that these devices do reduce embolic debris reaching the brain. (ii) Imaging studies using magnetic resonance imaging (MRI) scanning to identify brain injury have confirmed that nearly three quarters of patients had new brain lesions after TAVI, and that use of CEP devices was associated with reduced volume but not number of new lesions [13]. The significance of these clinically 'silent' lesions in the TAVI population remains uncertain, but they have been associated with cognitive decline and dementia in other studies [14]. (iii) Clinical evidence for the efficacy of CEP includes 4 randomised trials (described below), which were based on brain imaging surrogate endpoints, but also gathered clinical outcomes[15] [16] [17] [18], 2 clinical case-series [19] [20], and 2 systematic reviews [21,22]. Importantly these studies focussed on surrogate endpoints, were not powered for hard clinical endpoints, have reported outcomes at different times after TAVI, and include a range of CEP devices.

6.3. Previous research in CEP

6.3.1. Randomised Trials

The SENTINEL trial included 363 patients. The primary endpoint was new lesion volume on MRI scans. The study was neutral for an effect of CEP on the imaging endpoint, but did demonstrate a numerical trend toward stroke reduction from 9.1% to 5.6% (p=0.25). The CLEAN-TAVI trial included 100 patients[16]. The primary endpoint was based on MRI imaging. There was a reduction in new lesions and volume of lesions in the CEP group, but no reduction in neurological events (10% minor stroke in both groups). The DEFLECT III study, an exploratory study using MRI imaging included 85 patients[17]. There was a reduction in the

number of new lesions (21% to 11.5% in the CEP group), and a numerical reduction in in-hospital stroke from 5% to 2%. The MISTRAL-C trial included 65 patients and had an imaging based primary end-point[18]. There was a reduction in the proportion of patients with new lesions in the protected areas from 55% to 20% in the CEP group. This was associated with a numerical reduction in major stroke from 7% to 0% in the CEP group.

6.3.2. Observational studies

The University of Ulm series was an observational comparison of 280 consecutive patients treated with CEP to a historical propensity matched population. This single centre series demonstrated that stroke rates at 7-days were lower in the CEP group compared with the control group: 1% (4/280) compared with 5% (13/280), odds ratio (OR) 0.29, 95% CI 0.10 to 0.93, p=0.03. Mortality and stroke at 7-days was also significantly lower in patients with CEP than in the control group: 2% (6/280) compared with 7% (19/280), OR 0.30, 95% CI 0.12 to 0.77 (p=0.01).

6.3.3. Systematic reviews

A systematic review and meta-analysis of 1225 patients having TAVI (570 CEP and 655 control) showed that there was no statistical difference between groups for stroke within 72-hours of the procedure, the risk ratio (RR) of 0.53 suggested a potential benefit of cerebral protection (95% confidence interval (CI) 0.27 to 1.07, p=0.08) although the number of events was small (13/335 vs 15/180) and the statistical evidence was weak. More recently a further patient-level pooled analysis has been conducted combining the observational Ulm series and data from the randomised SENTINEL and CLEAN-TAVI trials (N=1306)[23]. Propensity matching allowed comparison of 533 patients who underwent TAVI with CEP to 533 without CEP. In patients undergoing TAVI with CEP there was strong evidence that stroke at 72 hours after TAVI and the combination of 72 hour mortality and stroke were reduced (10/533(1.88%) vs. 29/533 (5.44%), OR 0.35, 95% confidence interval (CI) 0.17–0.72, relative risk reduction 65%, p=0.0028 and 11/533 (2.06%) vs. 32/533 (6.00%), OR 0.34, 95% CI 0.17–0.68, relative risk reduction 66%, p=0.0013 respectively). These studies suggest a clinical effect of CEP in reducing early stroke with a number needed to treat of approximately 25. However caution is needed in interpreting these results because of the lack of power and heterogeneity in the included studies[24]. Indeed, two recent meta-analyses reach different conclusions on the efficacy of CEP highlighting the need to conduct a well-powered randomised controlled trial [21,25].

6.4. Why is the study needed now?

The evidence for the use of CEP has recently been assessed by National Institute for Health and Care Excellence (NICE) interventional procedure guidance committee (IPG 650), which concluded that there are no safety concerns over the use of CEP devices, but that the evidence on efficacy is inconclusive: It encouraged further research particularly to better understand patient selection and risk stratification[26]. We need high-quality evidence from an adequately powered randomised controlled trial to establish the safety, efficacy and cost-effectiveness of the technique and guide best practice in this important and expanding clinical field. CEP devices are not currently available in the NHS. BHF PROTECT-TAVI offers the unique opportunity within the NHS to test CEP devices in the general population of patients eligible for TAVI.

This trial will address the question of whether the routine use of CEP in TAVI reduces incidence of stroke in patients undergoing TAVI. This is a novel study because it is powered on a single clinically relevant outcome of stroke in an unselected TAVI population. This trial will address an important and unanswered clinical question which may impact future guidelines.

6.5. Stroke risk is not reduced with increasing experience

Increased TAVI volumes and institutional experience have contributed to reduced death and vascular complications, but this is not the case for stroke, which remains independent of experience and volume [27] [28]. Although the most recent randomised trials in patients at low surgical risk have suggested that TAVI may be superior to surgery, they were underpowered to detect a difference in stroke rates. Moreover, the

incidence of stroke has not reduced over time in registries of unselected patients. A recent analysis of the TVT registry analysed outcomes from over 100,000 TAVI procedures between 2011-17 and the risk of stroke remained constant over the 6-year period [29]. Furthermore, as TAVI is offered to younger and lower-risk patients, the longer term consequences of stroke are even greater over their lifespan given the reported impact on return to work, social activities and finances[30,31].

6.6. Stroke risk cannot be accurately predicted

Observational studies have identified the severity of aortic arch atheroma, smaller aortic valve area, degree of valve calcification, procedure time, advancing age, prior stroke, atrial fibrillation and renal impairment as risk factors for TAVI related stroke. The most comprehensive contemporary analysis from the TVT registry of nearly 100,000 procedures has developed a predictive model for TAVI related stroke. This confirmed the importance of prior stroke, age, peripheral vascular disease, chronic kidney disease, and smaller body habitus, but even with this large dataset the best predictive model had a modest predictive value with a C-statistic of only 0.62 [32].

7. OBJECTIVES AND OUTCOME MEASURES

PRIMARY OBJECTIVE	**OUTCOME MEASURES & TIMEPOINTS**
Does the routine use of CEP devices reduce the incidence of stroke associated with TAVI?	**Incidence of stroke** at 72 hours post-TAVI, or hospital discharge (if sooner)
SECONDARY OBJECTIVE	**OUTCOME MEASURES & TIMEPOINTS**
Does the routine use of CEP devices improve stroke, mortality, and cognitive/ disability outcomes?	**Combined incidence of all-cause mortality or non-fatal stroke** at 72 hours post-TAVI or hospital discharge (if sooner)
	Combined incidence of all-cause mortality, non-fatal stroke or transient ischaemic attack at 72 hours post-TAVI or hospital discharge (if sooner)
	Incidence of all-cause mortality at 72 hours post-TAVI or hospital discharge (if sooner)
	Win ratio for all-cause mortality, disabling stroke and non-disabling stroke at 72 hours post-TAVI, or hospital discharge (if sooner)
	Incidence of all-cause mortality at 12 months post-TAVI
	Incidence of all-cause mortality up to the end of the trial. This will use trial data up to 12 months, and centrally held NHS data from 12 months to the end of the trial
	Incidence of stroke as defined by centrally held NHS data (described in section 14.7) between 72 hours post-TAVI or hospital discharge (if sooner) and 30-days post-TAVI
	Incidence of stroke as defined by centrally held NHS data (described in section 14.7) between 30-days post-TAVI and the end of the trial

	Stroke Severity Assessed using the National Institutes of Health Stroke Scale (NIHSS) in participants who have had a stroke within 72-hours post-TAVI or hospital discharge (if sooner)
	Disability Outcome Assessed using the Simple Modified Rankin Scale questionnaire (smRSq) up to 12 months post-TAVI in participants who have had a stroke within 72-hours post-TAVI or hospital discharge (if sooner)
	Cognitive Outcome Assessed using the standardised Montreal Cognitive Assessment (MoCA) up to 12-months post-TAVI.
	Vascular access site related complications (VARC-2 criteria) at 72-hours post-TAVI or hospital discharge (if sooner) and between 6-8 weeks post-TAVI
Is the routine use of CEP devices cost-effective?	**Cost-effectiveness analysis** at 12 months

7.1. Primary outcome:

7.1.1. Incidence of all stroke at 72-hours after TAVI

The primary outcome is stroke at 72-hours (or at hospital discharge, if sooner) as this is the main clinical outcome that CEP might influence. From a mechanistic perspective, CEP will only impact on procedure-related embolic stroke.

7.1.2. Stroke and Transient Ischemic Attack definitions

Stroke will be defined as a new or worsened focal or global neurological deficit of presumed vascular origin, either ischaemic or haemorrhagic, occurring after randomisation and persisting for greater than 24 hours or leading to death. In this definition, a new stroke will not be defined exclusively by brain imaging, and a clinical deficit must be present for greater than 24 hours[33]. This will ensure a consistent definition of stroke across all enrolling sites not driven by the different availability of MR imaging in particular. In anticipation of changes in NHS Stroke Care Pathways over the lifetime of the trial, the definition of stroke will include those who have a mechanical thrombectomy for acute ischaemic stroke according to contemporary National Guidelines[34]. Patients who have identified occlusion of the cerebral vessels and undergo mechanical thrombectomy within 72-hour period after TAVI will be considered to have had a stroke outcome. This additional definition of stroke will allow the capture for the primary outcome of a small number of patients that have a complete neurological recovery as a result of that mechanical thrombectomy, and, therefore, will not meet the first definition.

Patients with a clinical deficit lasting less than 24 hours in duration, regardless of imaging evidence of infarction in the relevant vascular territory, will be defined as having a Transient Ischaemic Attack for the purposes of the secondary outcome analysis.

In keeping with other recent large clinical trials, stroke outcome ascertainment will be maximised by use of the validated 8-item question Questionnaire to Verify Stroke Free Status (QVSFS) on a daily basis in the 72 hours following the procedure, in addition to routine clinical review[35-37]. An answer of YES on the QVSFS since the procedure will prompt a local outcome assessment against the stroke definition as described above. The clinical diagnosis of stroke will be defined by local pathways including the stroke team as appropriate.

Initial stroke severity will be quantified by the National Institutes of Health Stroke Score (NIHSS), but a change score of 0 may still be compatible with a new stroke (for instance, a stroke causing a new deficit in the hand alone would score 0 on the NIHSS)[33].

The recovery and/or ongoing disability following stroke will be quantified using the modified Rankin Scale (mRS), the standard measure for assessing post-stroke disability. Sites will use the simple modified Rankin scale questionnaire (smRSq) preferably face-to-face to determine the mRS[38]. The advantage of this approach is that it may also be captured via postal questionnaire, or via telephone interview, thus minimising the likelihood of missing outcome data[39].

7.1.3. Adjudication of Primary outcome

The outcomes at 72-hours will be adjudicated by an independent Clinical Events Committee (CEC) using a standard protocol to limit bias (see section 17.3). The CEC will be blinded to trial treatment.

In addition to adjudicating the stroke outcomes, the CEC will be asked to identify a systematic approach to the identification of periprocedural hypotension so that its contributory role to any stroke outcome may be consistently applied. While most are expected to be embolic, there will be a small number of patients who have haemodynamic events for instance, following peri-procedure cardiac arrest. Any difference in stroke mechanism between the arms of the trial will be explored in the secondary analyses.

7.2. Key Secondary outcomes

1.Combined incidence of all-cause mortality or non-fatal stroke at 72 hours post-TAVI or hospital discharge (if sooner). Stroke will be assessed as defined in section 7.1.2.
2. Combined incidence of all-cause mortality, non-fatal stroke or transient ischaemic attack at 72 hours post-TAVI or hospital discharge (if sooner).
3. Incidence of all-cause mortality: at 72 hours post-TAVI or hospital discharge (if sooner)
4. **Win ratio for all-cause mortality, disabling stroke and non-disabling stroke** at 72 hours post-TAVI, or hospital discharge (if sooner)
5.Incidence of all-cause mortality: at 12 months post-TAVI.
6. Incidence of all-cause mortality: up to the end of the trial. This will use trial data up to 12 months, and centrally held NHS data from 12 months to the end of the trial
7. Incidence of stroke as defined by centrally held NHS data (described in section 14.7): Identified between 72 hours post-TAVI or hospital discharge (if sooner) and 30-days post-TAVI.
8. Incidence of stroke as defined by centrally held NHS data (described in section 14.7): Identified between 30-days post-TAVI and the end of the trial.
9. Stroke Severity: In participants who had a stroke within 72-hours post-TAVI or hospital discharge (if sooner) will be assessed using the National Institutes of Health Stroke Scale (NIHSS). This measure has been adopted as a secondary outcome to explore the association between use of the CEP and prevention of large cerebral vessel occlusion (LVO). Strokes with an NIHSS score of 10 or greater will be defined as severe.
10. Disability Outcome: Stroke recovery and/or ongoing disability in participants who had a stroke within 72-hours post-TAVI or hospital discharge (if sooner) will be assessed with the smRSq at discharge and between 6-8 weeks post-TAVI and at 12-months post-TAVI.
11. Cognitive Outcome: The standardised Montreal Cognitive Assessment (MoCA) detects mild cognitive impairment (MCI). It will be collected pre-procedure to establish the baseline measure. The telephone MoCA (without the items requiring the use of a pencil and paper or visual stimulus) is a valid and sensitive means of testing cognition following stroke and TIA. However, it is unable to measure visuoexecutive items; and, the performance of some domains (repetition, verbal fluency, and abstraction) performs less well over the telephone than with a face-to-face administration. However, it offers the opportunity to maximise the capture of this outcome assessment should face-to-face assessment prove not to be practical. Cognitive outcomes will be assessed up to 12 months post-TAVI.
The MoCA was collected from the start of recruitment in October 2020 and was discontinued from Version 5.0 of the protocol. The analysis for this outcome will be undertaken using all MoCA data collected until the implementation of Protocol Version 5.0.
12. Incidence of vascular access site related complications: Vascular complications will be recorded according to standard criteria defined by the Valve Academic Research Consortium (VARC-2) at 72-hours

post-TAVI or hospital discharge (if sooner) and between 6-8 weeks post-TAVI. Please go to http://onlinejacc.org/content/60/15/1438 for full details or see Appendix C[43].

13. Cost-effectiveness analysis: Data on quality of life and resource utilisation will be collected for a formal cost-effectiveness analysis. The validated EQ-5D-5L questionnaire will be used to assess quality of life.

8. TRIAL DESIGN

This is a prospective, open-label, outcome adjudicated multicentre randomised controlled trial (RCT) evaluating the use of a CEP device in participants with aortic valve stenosis planned for treatment by TAVI. TAVI will be carried out in specialist cardiac centres. Trial participants will be randomised with equal allocation to TAVI with CEP treatment or TAVI without CEP treatment (the current UK standard of care). Randomisation will be coordinated by the LSHTM CTU (London School of Hygiene and Tropical Medicine Clinical Trials Unit) via a secure website and stratified by centre using random permuted blocks.

8.1. Justification for all-comer study design

There are no statistical models to identify accurately a higher risk population that could inform a stratified approach. The trial will therefore allow a comprehensive assessment of the experimental treatment strategy in an unselected population and may subsequently inform the development of a risk prediction model.

8.2. Study population

At each participating centre all patients with aortic stenosis who are scheduled for TAVI will be considered for the trial. The technical suitability for the use of CEP will be left to the discretion of the treating physician. Relative contra-indications to the use of CEP include severe proximal stenosis or congenital variation of the anatomy of the left common carotid and right brachiocephalic arteries (e.g. complex non-standard anatomy such as bovine arch or aberrant right subclavian), or no vascular access options via the right upper limb. In order that this population reflects a general population of patients with aortic stenosis who are considered suitable for TAVI we have identified no other specific exclusion criteria.

9. PARTICIPANT IDENTIFICATION

9.1. Trial Participants

The target population for this trial is patients with severe aortic stenosis undergoing treatment by TAVI.

9.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial
- Aged 18 years or above
- Considered to be candidates for TAVI by the clinical team (via any access route where CEP may be used)
- Participant is suitable for treatment with the cerebral embolic protection device in the opinion of the treating physician.

9.3. Exclusion Criteria

We have identified no specific exclusion criteria. Participants involved in observational studies will be eligible for this study. As this is an all-comer design, current or previous participation in other ongoing randomised trials will not be disqualifying for recruitment to this study unless treatment is expected to impact on the effect of using a CEP device on stroke.

10. TRIAL PROCEDURES

10.1. Screening and Eligibility Assessment

The clinical team at the recruiting centres (Participating centres and participant identification centres) will consider all patients who are considered to be candidates for TAVI by the supervising clinician.
Screening will take place prior to consent and randomisation. It will be done by the treating clinical team (or delegated member of the direct care team) using patient notes. There will be no access by the research team to patient identifiable data prior to consent.

10.2. Informed Consent

Only patients who give consent will be included in the trial. If informed consent is not possible, the patient will not be recruited into the trial. Consent will be taken prior to the patient's scheduled TAVI procedure. The patient will be allowed as much time as wished to consider the participant information sheet and the opportunity to question the Investigator, or other independent parties to decide whether to participate in the trial.

If possible, Informed Consent will be obtained in writing by means of a patient dated signature and a dated witness signature of the person who presented the Informed Consent Form.

Oral consent (over the telephone or by videoconference) is also permissible. This will be documented using the approved remote consent form. Baseline data can be collected once consent has been recorded in this manner. However, the participant must personally sign and date the remote consent form to confirm their participation in the trial when they attend hospital. They must sign and date the form before randomisation can take place.

The person who obtained the consent must be suitably qualified and experienced, have been authorised to do so by the Chief/Principal Investigator and authorisation documented on a trial delegation log. One copy of the signed Informed Consent Form will be given to the participant, one copy will be kept in the local trial site file and the original will be placed in the patient's medical records.

For the purposes of informed consent monitoring, redacted consent forms may be requested by the LSHTM CTU and will be sent by secure email.

10.3. Randomisation

Randomisation of consenting patients will be performed following consent by the staff delegated by the local PI to be responsible for randomisation at each hospital using a web-based randomisation system (Sealed Envelope). Best practice is for randomisation to be carried out as near as possible to the time of the patient's scheduled TAVI procedure. However, randomisation must be performed before the start of the TAVI procedure which is defined as first arterial puncture.
Randomisation will be done as follows:
The delegated member of staff will access the randomisation system at sealedenvelope.com

- They will confirm the eligibility criteria for the patient (see section 9.2 and 9.3):
- To complete randomisation of the patient, the delegated member of staff will need to enter their password and click "Confirm. This will generate the treatment allocation to either TAVI (standard of care) or TAVI with CEP (intervention). The allocation will be received as an on-screen notification and via email to the investigator. This information will be directly available to the doctor performing the TAVI and, if allocated, the CEP implementation.
- Randomisation will create the CRF record for the patient and will automatically be logged.

10.4. Access to the online randomisation service

Access to the randomisation site sealedenvelope.com will only be available to staff delegated by the local PI (Principal Investigator) to be responsible for randomisation. Delegation and training logs will be recorded at both the local research team and at the LSHTM CTU. Randomisation training includes a demonstration of the system and training in the trial eligibility criteria. These will be provided at the site initiation visit in the first instance, and then locally by previously trained staff for newly delegated researchers. Each staff member will have a unique account for accessing the randomisation site, and must not share these details of their account with other staff members.

If a staff member is unable to access their account, they can follow the password reset instructions on sealedenvelope.com or contact the LSHTM CTU to request an account reset at bhfprotect-tavi@LSHTM.ac.uk. Please note that the LSHTM CTU is available for account resets between the hours of 8am – 5pm, Monday to Friday.

10.5. Blinding and code-breaking

Unblinded staff:

This is an open-label trial. Hospital staff will be aware of the allocation of patients.

Blinded trial staff:

As an open-label trial there will be no blinded staff. However, the clinical events committee will be blinded to trial treatment. Supporting documentation sent to the committee will be redacted by staff at the LSHTM CTU.

10.6. Trial procedures table

	Visit T-2: Initial patient approach (e.g.: clinical visit*)	Visit T-1: Informed consent obtained, baseline assessments (Clinical or study visit)	TAVI procedure (Clinical visit)	During hospital admission for TAVI**			Visit 1: In person (clinical visit) or by phone (study visit)	Visit 2: In person (clinical visit) or by phone (study visit)
			Day 0	**Day 1**	**Day 2**	**72-hours post-TAVI or discharge if sooner**	**6-8 weeks post-TAVI**	**12-months post-TAVI**
Eligibility assessment (clinical care team)	**X**							
Informed consent		**X**						
Baseline assessments		**X**						
Randomisation			**X**					
TAVI with CEP (intervention arm) OR TAVI without CEP (standard of care)			**X**					
Stroke status assessed by clinical team review				**X**	**X**	**X**		
Questionnaire to Verify Stroke Free Status (QVSFS)				**X**	**X**	**X**		
National Institute of Health Stroke Score (NIHSS)***						**X**		
Simple modified Rankin scale questionnaire (smRSq) ***		**X**				**X**	**X**	**X**
Stroke physician assessment***				**X**	**X**	**X**		
Mortality status						**X**	**X**	**X**
Vascular access site injury						**X**	**X**	
EQ-5D-5L		**X**					**X**	**X**
Adverse event reporting			**X**	**X**	**X**	**X**	**X**	
API Study questionnaire****						**X**		

* Clinic visit refers to non-study visits. These are routine hospital attendances as part of standard care.

** During the patient's in-hospital stay the QVSFS will be administered daily up to and including 72 hours or discharge from hospital, whichever is earlier.

*** Only be administered if the participant's QVSFS indicated the possible presence of a stroke.

****Only for BHF PROTECT-TAVI participants who consent to take part in the API Study

10.7. Baseline assessments

Visit T-2 Initial patient approach at pre-procedure visit (done by clinical care team)

- Eligibility assessment (prior to visit)
- Patient information sheet provided if patient eligible
- Patient invited to join study

Visit T-1 Informed consent and baseline data collection (during clinical visit or study visit either in person or over the telephone/videoconference)

Baseline data can be collected at any time from consent up to the time of the patient's TAVI procedure.

- Informed consent collected
- Demographics
- Medical history
- Upload standard of care imaging (CT and echo)
- Concomitant medications
- smRSq
    - Short questionnaire administered for the study
- EQ-5D-5L
    - Short questionnaire administered for the study

TAVI Procedure

- Randomisation (this will be done by the cardiologist or other delegated staff member)
- The start of the TAVI procedure is defined as first arterial puncture.
- TAVI with CEP (intervention arm)
    - The TAVI procedure takes approximately 90 minutes and is done by a cardiologist. The CEP adds approximately 5 minutes to the procedure and is done by the cardiologist.
- TAVI without CEP (standard of care) (control arm)
    - The TAVI procedure takes approximately 90 minutes and is done by a cardiologist.

10.8. Subsequent visits

Please refer to section 10.6 for the table of trial procedures.

10.8.1. In hospital

This will be carried out daily up to and including 72 hours post-TAVI, or until discharge if sooner.

Primary outcome

- Stroke status
    - Assessed by routine clinical assessment post-TAVI, supported by the framework provided by the QVSFS.
        - If after routine clinical assessment, the participant is reviewed by the local stroke team, a Stroke Form must be completed.
    - If the participant answers YES to any of the questions on the QVSFS, this will prompt a local outcome assessment against the stroke definition described in section 7.1.2. and the diagnosis will be recorded on the Stroke Form in the eCRF, with supporting information as required. If a stroke is diagnosed by the stroke team, severity is assessed using NIHSS and recovery is assessed using smRSq
        - Short questionnaires administered for the study

Secondary outcomes

- Mortality status
    - Taken from patient notes
- Vascular injury
    - Taken from patient notes

- Safety reporting
    - Taken from patient notes

The API Study

The API Study Questionnaire is only completed by participants who have consented to take part in the API study (see Section 12). The questionnaire is self-administered and should be completed following the patient's TAVI procedure up to 72 hours post-TAVI or hospital discharge (if sooner).

10.8.2. Visit 1 – 6-8 weeks post-TAVI

This will be conducted by telephone for the study, however if there is a pre-scheduled clinical visit, it can be done in person.
Contact with the patient will be arranged by a delegated member of the research team at the local hospital. Phone calls are projected to take no more than 10 minutes to complete the EQ-5D-5L questionnaire. The staff contacting the patient will check electronic records prior to contacting the patient to ensure they have not died. While participant preferences for contact will take priority, we advise that after 3 unsuccessful attempts to reach the patient no further attempts are made.

Secondary outcomes assessed:

- Mortality status
    - Taken from patient notes
- smRSq
    - Short questionnaire administered for the study (only done in presence of a stroke outcome)
- EQ-5D-5L
    - Short questionnaire administered for the study
- Vascular injury
    - Taken from patient notes
- Safety reporting
    - Taken from patient notes

10.8.3. Visit 2 – 12 months post-TAVI

This will be conducted by telephone for the study, however if there is a pre-scheduled clinical visit, it can be done in person.
Contact with the patient will be arranged by a delegated member of the research team at the local hospital. Phone calls are projected to take no more than 10 minutes to complete the EQ-5D-5L questionnaire. The staff contacting the patient will check electronic records prior to contacting the patient to ensure they have not died. While participant preferences for contact will take priority, we advise that after 3 unsuccessful attempts to reach the patient, no further attempts are made.

Secondary outcomes assessed:

- Mortality status
    - Taken from patient notes
- smRSq
    - Short questionnaire administered for the study
- EQ-5D-5L
    - Short questionnaire administered for the study

10.9. Sample Handling

No additional samples will be taken as part of this research study.

10.10. Participant withdrawal

According to the design of the trial, participants have the following three options for withdrawal;

1) Participants may withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., CT-Scans, blood results and disease progression data etc.
2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis. (Any limits to this type of withdrawal where, for example analysis of their data has already been integrated into interim results will be explained in the participant information sheet).

The type of withdrawal and reason for withdrawal, if known, will be recorded in the CRF (Case Report Form). Withdrawal from the trial will not influence future healthcare in anyway.

10.11. Definition of End of Trial

The end of the trial is the date of the last completed 12-month follow-up visit (Visit 2 in section 10.8.3)

11. TRIAL INTERVENTIONS

11.1. Intervention: TAVI with CEP

The device group will have TAVI performed with CEP. The Claret Sentinel dual-filter device (Boston Scientific, MA, USA) is a single use, embolic protection catheter inserted into the right radial or brachial artery. This is the only device currently approved for use in both Europe and the USA, and has the largest body of clinical evidence. The device employs two filters (nitinol frames with 140-micron pores polyurethane film), one delivered to the brachiocephalic artery (Proximal Filter), and one to the left common carotid artery (Distal Filter) before TAVI. Following the TAVI procedure the system is removed.

11.2. Control: TAVI without CEP (standard of care)

The control group will have standard of care as routine for the TAVI without the use of CEP. There is no blinding of the procedure for the operators involved in the trial.

11.3. Discontinuation of the trial treatment

The physician performing the patient's TAVI procedure can discontinue the patient's treatment at any time in accordance with their clinical judgement. These patients will remain in the study and be included in the intention to treat analysis according to the arm to which they were randomised.

11.4. CEP device details

The CEP Claret Sentinel dual-filter device will be provided free of charge to participating hospital sites. To receive the Claret Sentinel dual-filter device the participating hospital must complete standard training and be approved by the company to use the CEP device. Each site will receive 10 devices for training purposes. Provision of devices to sites is covered in the site agreement.
The Claret Sentinel dual-filter device will be used as marketed under its CE mark for this study.
Adverse events will be captured as described in section 13.

12. ASSESSING THE QUALITY OF PATIENT INFORMATION IN THE BHF PROTECT-TAVI TRIAL (API STUDY)

12.1. Study design

The API Study is an observational, non-randomised study to assess the quality of information given to BHF PROTECT-TAVI trial participants about the trial prior to consent. Data are collected via a self-administered, paper questionnaire completed by trial participants. The API Study is an optional study open to all BHF PROTECT-TAVI participating sites. The API Study will recruit a maximum of 300 participants. The start and end date of the study will be confirmed by the LSHTM CTU.

12.2. Objectives

- To examine how participants evaluated each source of information they received about the study in understanding the different aspects of trial participation
- To determine which source(s) of information participants found most helpful

12.3. Outcome

Participant-reported perception of BHF PROTECT-TAVI trial information.

12.4. Study participants

At each participating centre, all patients enrolled in the BHF PROTECT-TAVI trial will be considered for the API Study. There are no specific exclusion criteria.

12.4.1. Inclusion criteria

- Patients who have consented to participate in the BHF PROTECT-TAVI trial
- Patients who are willing and able to give informed consent for participation in the API Study

12.4.2. Exclusion criteria

The are no exclusion criteria for the study.

12.5. Screening and eligibility assessment

Patients are approached following their TAVI procedure up to 72 hours post-TAVI or hospital discharge (if sooner).

12.6. Informed consent

BHF PROTECT-TAVI trial participants will be given a copy of the API Study patient information sheet. Written Informed Consent will be obtained by means of a patient dated signature and a dated witness signature of the person who presented the Informed Consent Form. One copy of the signed Informed Consent Form will be given to the participant, one copy will be kept in the local trial site file and the original will be placed in the patient's medical records.

12.7. Data collection

Once consented, participants will be given the paper questionnaire to complete. The questionnaire takes approximately five minutes to complete and is only available in English. Participants' BHF PROTECT-TAVI study ID will be entered on the questionnaire by site staff. This is to allow linkage with demographics data (month and year of birth, gender, ethnicity) collected for the BHF PROTECT-TAVI trial. Participants will also have the option to provide their email address or phone number so they can be contacted by the trial team to discuss their responses.

The completed questionnaires should be scanned by the research staff at the site and emailed to the LSHTM CTU. The electronic copies will be deleted once the questionnaires have been printed. Printed copies will be stored securely in the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine

12.8. Participant withdrawal

A participant may decide to withdraw from the API Study at any time and this will not affect their participation in the BHF PROTECT-TAVI trial or the care they receive.

12.9. Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018. The processing of the personal data of participants will be minimised by making use of a unique participant study number only. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Participants have the option to provide their contact details. These will be stored securely in a locked cabinet within a room which is locked in the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine in accordance with UK General Data Protection Regulation (GDPR). The data will not be kept longer than necessary and will be deleted within three months after the end of the BHF PROTECT-TAVI trial.

12.10. Funding

No additional funding is required for the API Study.

12.11. Dissemination

Results will be disseminated through publications, conferences and directly to patients involved in the study.

13. SAFETY REPORTING

13.1. Adverse Event Definitions

Non-Serious Adverse Event (NSAE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product but which are not considered to be serious as defined below.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect*. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "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.
Assessment of Causality	The relationship of each adverse event to the trial treatment must be determined by a medically qualified individual according to the following definitions: **Probably related:** A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the adverse event and the treatment **Possibly related:** A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the adverse event and the treatment **Unlikely related:** A causal relationship is improbable and another documented cause of the adverse event is most plausible. **Unrelated:** A causal relationship can definitely be excluded and another documented cause of the adverse event is most plausible.
Clinical trial activities	Any events that occur as a result of trial specific activities relating to the participant's involvement in the trial. This includes: • any complications relating to the CEP device • any time delays to treatment or extension of procedural duration • any other events that occur as a result of trial specific activities (such as follow-up)

13.2. Site reporting procedures for Serious Adverse Events to the CTU

The following procedure should be followed by site study teams for the reporting of Serious Adverse Events (SAEs).

- SAEs are reported up to the 6-8-week follow-up timepoint.
    - Expected events are defined as any of the outcomes (see Section 7) or recognised complications of TAVI surgery and CEP use (see Section 13.4). These events should be reported in the eCRF up to discharge and do not need to be reported separately as adverse events. Post-discharge, recognised complications of TAVI surgery and CEP use do not need to be reported.

- Causality will be assessed by the Principal Investigator at each site (as defined in section 13.1).
- Events which, in the opinion of the Principal Investigator, are unrelated to clinical trial activities do not need to be reported.
- Site study teams will report unexpected SAEs (i.e. any not listed in section 7 or 13.4) that are *possibly, probably or unlikely to be* related to clinical trial activities (as defined in section 13.1) using the secure, password protected trial database within 7 days of the site study team becoming aware of the event.
- The site study team will provide additional, missing or follow up information in a timely fashion as requested.

13.3. Reporting of related Serious Adverse Events to the Sponsor and REC

The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of patients or impact on the conduct of the trial. Notification of confirmed unexpected and related SAEs will be to the Sponsor and the REC within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). Events that are classified as probable and possible will be treated as related for the purposes of AE reporting.

13.4. Events exempt from immediate reporting as SAEs

The following events are recognised complications of TAVI surgery and CEP use. They do not need to be reported separately as adverse events, but should be reported as part of the CRF.

13.4.1. TAVI

1) Acute Coronary Syndrome ACS
2) Acute Kidney Injury
3) Angina
4) Aortic dissection
5) Aortic rupture
6) Arrhythmia
7) Arteriovenous fistula
8) Atelectasis
9) Bleeding, operative or post-operative
10) Cardiac Arrest
11) Cardiac Tamponade
12) Cardiogenic Shock
13) Complications of suicide ventricle
14) Conduction system injury (with or without temporary or permanent pacing)
15) Congestive Heart Failure (CHF)
16) Death
17) Delirium
18) Endocarditis
19) Embolism, including air
20) Gastrointestinal (GI) bleed
21) Hematoma
22) Ischemia (coronary, limb, carotid)
23) Infection (local or systemic)
24) Myocardial Infarction (MI)
25) Nerve injury
26) Pain at access site
27) Paravalvular leak
28) Pericardial effusion
29) Pulmonary oedema
30) Pulmonary embolism

31) Right Ventricular Failure (RVF)
32) Severe LV dysfunction
33) Stroke
34) Vascular injury (e.g., dissection, rupture, perforation, pseudoaneurysm)

13.4.2. CEP

1) Complications at the site where the device is introduced (this will either be an artery at the wrist or elbow), such as bleeding, blood vessel injury (e.g. dissection, rupture, perforation, pseudoaneurysm), nerve injury, haematoma (large bruise)
2) Aortic, brachiocephalic or carotid artery dissection
3) Kidney injury (due to the need for additional administration of radiographic contrast medium)

13.5. Reporting procedures for Non-Serious Adverse Events

- Events which are expected complications of TAVI surgery and CEP use do not need to be reported separately as adverse events, but should be reported as part of the CRF (see section 13.4)
    - Post-discharge, recognised complications of TAVI surgery and CEP use do not need to be reported.
- Site study team will report unexpected Non-Serious Adverse Events (NSAEs) that are possibly or probably related to clinical trial activities as defined in section 13.1) using the secure, password protected trial database within 14 days of the site study team becoming aware of the event.
- NSAEs are reported up to the 6-8-week follow-up timepoint.
- The site study team will provide additional, missing or follow up information in a timely fashion if requested.
- The Chief Investigator will review reported AEs for causality as defined in section 13.1.

14. STATISTICS

Statistical analysis will be coordinated from the Clinical Trials Unit at London School of Hygiene and Tropical Medicine.

14.1. Statistical analysis and methods

A detailed statistical analysis plan (SAP) will be produced prior to unblinding of any data. In summary, the primary analysis will be a comparison of the incidence of stroke at 72-hours after TAVI between patients randomised to receive CEP and patients randomised to TAVI without CEP (standard care). A risk ratio and 95% confidence interval (CI) will be calculated together with a p-value. The event rate is expected to be low and the absolute impact of CEP will also be assessed with a risk difference and 95% CI. The primary analysis will be on an intention to treat basis. Secondary clinical outcomes will be analysed using the above approach. In addition, a multivariable logistic regression model will be developed to identify those patients at higher underlying risk of a stroke at 72 hours. Details will be provided in the SAP but briefly independent risk factors will be identified and a patient's individual risk for a stroke will be calculated. In order to assess the effect of CEP by risk, patients will be categorised according to their underlying risk of a stroke. The percentage of patients with stroke will be tabulated by treatment group and risk category along with absolute risk differences, to consider whether the impact of CEP depends on underlying risk.

14.2. Sample Size Determination

If the proportion experiencing the primary outcome is 3% in the control arm, we will require 7652 patients to detect a 33% relative risk reduction (risk ratio 0.67) to 2%. Assuming 1% losses/withdrawals we will recruit 7730, for 80% power and 5% significance. For the secondary combined outcome of all-cause mortality or stroke at 72 hours, a trial of 7730 would also provide very good power. For example, for a 33% relative reduction from a combined rate of 4.2% a trial of 7730 would provide power well in excess of 90%.

The event rate for the primary outcome is based on a review of published data from randomised trials and registries. Self-reported stroke rates in registries are less than those reported in randomised trials, where there is more active stroke ascertainment. A recently published patient level analysis reported a 72-hour stroke rate of 5.4% in the control group, and the recently published meta-analysis shows stroke rates of 6%. In the UK registry the self-reported incidence was 2.6% in 2017. We believe that by using a structured approach using the QVSFS the stroke ascertainment rate is likely to be higher. We have been conservative in our predicted event rate for all stroke at 3%, which is still nearly half of that reported in previous randomised TAVI trials.
Previous published studies suggest a potentially large impact of CEP on reducing incidence of stroke. However, these are not based on well-powered randomised trials and may overestimate efficacy. Therefore, the proposed effect size is based on more conservative estimates in comparison to data published from observational studies or small-randomised trials, while still representing a clinically meaningful reduction in stroke.

14.2.1. Sample size increase

To maximise the chance of delivering a definite result for the trial, the sample size was increased from 7730 to 9712.

14.3. Analysis Populations

The primary analysis of the trial will be on an intention to treat basis, including all participants whose TAVI procedure is started according to the group to which they were randomised irrespective of whether they received the intervention as allocated. In addition, a per protocol analysis and complier average causal effect analysis will also be performed. Full details will be included in the separate Statistical Analysis Plan.

14.4. Stopping criteria

The following decision points and interim analyses are built into the trial design:
Milestone 1: Feasibility of recruitment 24 months after trial commences: We will assess feasibility 24 months after the trial commences using the following criteria:

1. Completed set up of at least 20 sites
2. Randomised at least 80 participants per month over the preceding 3 months
3. Randomised at least 800 participants in total

If these targets are not met, then the Trial Steering Committee and BHF will consider the feasibility of continuing the trial.
Milestone 2: The first interim analysis will be after 50% of patients (3865 patients) have completed follow-up for the primary event.
Milestone 3: The second interim analysis will be after 70% of patients (5411 patients) have completed follow-up for the primary event.
Milestone 4: Due to the increase in the sample size, a third interim analysis will take place once 134 primary outcome events have occurred.
Interim analysis (Early stopping criteria for efficacy or futility): The Data Monitoring Committee (DMC) will be convened to monitor the safety of patients and perform interim analyses at Milestones 2, 3 and 4 to assess futility and efficacy. Interim analyses may lead to the early closure of the trial following consultation with the Trial Steering Committee (TSC), Sponsor and Funder. Other outcome and safety data would be considered by the DMC in making their recommendation.
The Level of Statistical Significance
The trial is designed to assess the primary outcome with 80% power and 5% significance.

14.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

All patients randomised to the trial will be analysed on an intention-to-treat basis. Data will be validated through data review and querying, and the data analysis will take appropriate account of missing values. This process will be detailed in the statistical analysis plan.

14.6. Health Economics Analysis

A cost-effectiveness model will be developed to estimate the short-term (1-year) and longer-term (lifetime) survival and quality-adjusted life years (QALYs) and the costs incurred by the NHS and Personal Social Services (PSS). The analysis will also address whether value for money could be further optimised within the overall TAVI population (e.g. using additional risk stratification). In addition to the primary and secondary trial endpoints, we will prospectively link the trial participants to collect further data until the end of their participation in the trial on subsequent stroke and other events (from Hospital Episode Statistics [HES], hospital resource utilisation [HES] and mortality (Office for National Statistics [ONS]). The linkages to HES and ONS will provide a more complete picture of the short and longer-term costs and outcomes and will enhance the precision and robustness of the cost-effectiveness results. Resource utilisation during the initial index admission will be collected. This will include information on the duration of the procedure, any additional procedures and consumables and the duration of the initial index admission (including any periods in ICU). To estimate healthcare costs, we will assign national average costs using NHS Reference costs and PSSRU (Personal Social Services Research Unit) unit cost estimates. We will collect quality of life measures using the standardised EQ-5D-5L at baseline and at 12 months to estimate QALY changes over the 12-month follow-up. The longer-term model will extend the time horizon to a lifetime. The model will take into account uncertainty in the evidence base (including risk of events, outcomes and costs). Our results will determine the probability of CEP being cost-effective, conditional on various levels of willingness-to-pay values for gain in health benefit. Sensitivity analyses will be conducted to evaluate the impact of alternative model assumptions.

14.7. Use of centrally held data to assess long-term stroke and mortality follow-up in patients recruited at NHS sites.

To assess long-term stroke and mortality outcomes, we will link trial participants recruited at NHS sites to Hospital Episode Statistics (HES) and mortality data held by NHS England other central UK NHS bodies and the Office for National Statistics (ONS). Participant's NHS number and their date of birth or their Community Health Index will be shared securely between the London School of Hygiene & Tropical Medicine/University of Oxford and NHS England/other central UK NHS bodies /Office for National statistics (ONS) via secure email in order to request the health outcome data of participants. NHS England/other central UK NHS bodies /ONS will return the requested information to the London School of Hygiene & Tropical Medicine/University of Oxford in pseudo-anonymised form which is only identifiable to the data controller. The data will be held in a secure database on the server at the London School of Hygiene and Tropical medicine. Researchers at the University of York and The Newcastle upon Tyne Hospitals NHS Foundation Trust will be given access to the secure server to undertake analyses for the trial.

15. DATA MANAGEMENT

The plan for the data management of the study is outlined below. For further information please refer to the data management plan.

15.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. EQ-5D-5L where there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

15.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

15.3. Data Recording and Record Keeping

All trial data will be entered into an electronic CRF managed by Sealed Envelope Inc and hosted by Rackspace. In accordance with ICH GCP (International Conference on Harmonisation Good Clinical Practice), Section 5.5, this electronic data entry system has been validated and Standard Operating Procedures (SOPs) covering its use are maintained.
The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.
Personal patient data that is not part of the research record (i.e., consent forms) will be deleted as soon as possible following the conclusion of the study.
Data will not contain any identifiable data, apart from NHS number which will be encrypted and stored separately from the other data. This will be used to link patients to HES data through NHS Digital.

15.4. Transfer of imaging data including CT scans and MRIs

Baseline CT imaging, and CT and MRI for patients with a suspected stroke will be sent to the University of Oxford core lab either by web upload using a secure website or directly through the sites PACS system. The images will be transferred securely from the participating site to Caristo Diagnostics Ltd with the participant's unique identification number, and no identifiable details and then transferred to the University of Oxford. Once the core lab at the University of Oxford has download the data, Caristo Diagnostics Ltd will purge the data stored on the system.

Alternatively, anonymised imaging can be copied to a disc/hard drive and posted to the lab.
Images collected may be used to support other research in the future and may be shared anonymously with other researchers.

16. QUALITY ASSURANCE PROCEDURES

16.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and SOPs. A risk assessment and monitoring plan will be prepared before the study opens for recruitment and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

16.2. Monitoring

The conduct of the trial will be supervised by trained staff from the LSHTM CTU. The trial will be monitored on a regular basis using central statistical monitoring. On-site monitoring will take place if considered necessary by the LSHTM CTU or if requested by the trial site.
Local investigators shall ensure that all trial data are available for trial related monitoring, audits and research ethics committee review.
The CTU will periodically monitor consent forms to ensure that the consent procedure is being correctly followed.

17. TRIAL COMMITTEES

17.1. Trial Steering Committee (TSC)

17.1.1. Role of the TSC

The TSC provides overall supervision of the trial. In all the deliberations of the Trial Steering Committee, the rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.
The functions of the TSC are:

1) to provide trial oversight and supervision on behalf of the Sponsor and Funder;
2) to monitor and supervise the progress of the BHF PROTECT-TAVI Trial towards its interim and overall objectives;
3) to ensure compliance with Guidelines for Good Clinical Practice;
4) to review at regular intervals relevant information from other sources (e.g., other related trials);
5) to consider the recommendations of the Data and Safety Monitoring Committee (DMC);
6) to report to the Sponsor and the British Heart Foundation (BHF) on progress of the trial
7) to advise Chief Investigator (CI), Sponsor and Funder on all aspects of the trial.

The TSC will meet as frequently as required, at least annually, for the duration of the trial. Please reference the TSC charter for further information.

17.1.2. TSC Membership

Dr Rob Henderson (Trent Cardiac Centre) – Chair
Bernard Bryan (Patient representative) - Independent
Priscilla Coley (Patient representative) – Independent
Dr Darren Mylotte (Galway Hospital) – Independent
Professor Nikola Skipper (Nottingham University) - Independent
Professor Rodney Stables (Liverpool Heart & Chest Hospital)
Professor Rajesh Kharbanda (John Radcliffe Hospital) – Chief Investigator
Professor James Kennedy (John Radcliffe Hospital) – Co-Chief Investigator
Professor Tim Clayton (LSHTM) – Co-investigator

17.2. Data Monitoring Committee (DMC)

17.2.1. Role of the DMC

The DMC examine the data accumulated during progress of the BHF PROTECT-TAVI trial and ensure that the benefit/risk balance remains acceptable for participating patients. It is the only committee which will have access to data broken down by treatment during the trial and on this basis, the primary responsibility of the DMC is to review interim analyses of outcome data and to recommend to the Trial Steering Committee (TSC) whether the trial needs to be changed or terminated based on these analyses.
More specifically, the duties of the DMC will include:

1) monitoring evidence for treatment differences in the primary and secondary outcomes
2) monitoring evidence for treatment harm (e.g. deaths, adverse events)
3) assessing the impact and relevance of external evidence
4) deciding whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
5) assessing data quality, including completeness

6) reviewing recruitment figures and monitor losses to follow-up
7) monitoring compliance with the protocol by participants and investigators
8) monitoring continuing suitability of patient information
9) monitoring compliance with previous DMC recommendations

The DMC will meet as required.

17.2.2. DMC Membership

Professor Colin Berry (University of Glasgow) - Chair
Professor Jesse Dawson (University of Glasgow)
Professor Chris Rogers (University of Bristol)
Mr Matthew Dodd (Unblinded statistician, LSHTM)

17.3. Clinical events committee (CEC)

17.3.1. Role of the CEC

The CEC will review the blinded reported stroke events which make up the primary and secondary outcomes. The criteria and working order of the CEC will be determined by the members and established in a signed charter. All committee members will be blinded to the treatment group.
The CEC will provide a consistent assessment of the outcome events across all sites.

17.3.2. CEC Membership

Professor Andrew Demchuk (University of Calgary)
Professor Anna Poggesi, (University of Florence)
Professor David Thaler (Tufts Medical Centre)

17.4. Trial Management Group

17.4.1. Membership

Professor Rajesh Kharbanda (John Radcliffe Hospital)
Professor Tim Clayton (LSHTM)
Professor James Kennedy (John Radcliffe Hospital)
Mr Richard Evans (LSHTM)
Ms Zahra Jamal (LSHTM)
Ms Kiran Bal (LSHTM)

18. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.
It is the responsibility of the local site PI to report any suspected protocol deviations to the BHF PROTECT-TAVI CTU within 7 days of the suspected deviation becoming known.

19. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree;
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial".
In the event that a serious breach is suspected, the Sponsor and Chair of the TSC must be contacted within one working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

20. ETHICAL AND REGULATORY CONSIDERATIONS

20.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

20.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

20.3. Approvals

Health Research Authority and Wales Research Ethics Committee 5 have reviewed and approved the study. The REC number is 20/WA/0121
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

20.4. Other Ethical considerations

20.4.1. Efficacy or futility

There are ethical issues in enrolling patients into a trial that is either showing a very clear benefit to patients or demonstrating an increased risk to patients. Further, a trial needs to recruit sufficient patients to achieve the sample size in the time and budget provided. To address these issues, we have built in a series of check-points that will assess whether the trial is meeting recruitment targets. We plan to stop recruitment if it becomes clear that not enough patients can be enrolled to complete the trial successfully. Furthermore, an independent Data Monitoring Committee (DMC) will be established to review interim analyses and assess benefits and risks to patients in either arm. A DMC Charter will be developed which will contain details of the functioning of the DMC including any pre-defined stopping guidelines.

20.4.2. Language

Currently, the patient documents and study questionnaires are only available in English. Copies of these documents will be made available in Welsh on request. The animated participant information video is available is Bengali, English, Hindi, Polish and Turkish.

20.4.3. Intervention risk

There are small risks associated with CEP including slightly increased exposure to radiation, vascular injury, infection at the insertion point and bleeding. However, the available evidence has recently been assessed by National Institute for Health and Care Excellence (NICE) interventional procedure guidance committee (IPG 650), which concluded that there are no safety concerns over the use of CEP devices, but that the evidence for clinical efficacy is inconclusive. Therefore, it encouraged further research particularly to better understand patient selection and risk stratification. There is a need for high-quality evidence from

an adequately powered randomised controlled trial to establish the safety, efficacy and cost-effectiveness of the technique and guide best practice in this important and expanding clinical field. This trial will provide this evidence.

20.4.4. Contact in case of participant death

It is important that follow-up contact is not attempted for patients who have passed away since the last time of contact. Therefore, research staff conducting follow-up will check patient records to confirm that the patient is alive prior to contacting them.

20.4.5. Incidental Findings

Should any findings of clinical significance be discovered, they will be referred to the doctor in charge of patient care for clinical verification.

20.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, the BHF and University of Oxford. In addition, an End of Trial notification and final report will be submitted to the REC, funder, host organisation and Sponsor.

20.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

20.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the paper CRF, where participant initials may be added, which will be kept at the local site only. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

21. FINANCE AND INSURANCE

21.1. Funding

Funding for this study is provided by the British Heart Foundation.

Funding for the CEP devices is provided by Boston Scientific, Inc. who will have no involvement in the academic coordination and conduct of the study.

21.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided. For patients recruited at private hospitals, any harm to participants that arises from their clinical treatment provided will be covered by the private hospital's indemnity.

21.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

22. PUBLICATION POLICY

22.1. Policy

Publications will follow the CONSORT guidelines. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the British Heart Foundation. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

22.2. Dissemination

Results will be disseminated through publications, conferences and directly to patients involved in the study. The patient focussed results dissemination documents will be developed in collaboration with patient representatives on the TSC and the LSHTM CTU Patient Research Advisory Group.

23. INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University of Oxford. will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

24. ARCHIVING

Trial materials will be archived centrally and locally as coordinated by the BHF PROTECT-TAVI CTU for 15 years. Local archiving of trial materials at participating sites will follow local procedures. Archiving of central trial materials will be done through the LSHTM's archiving service.

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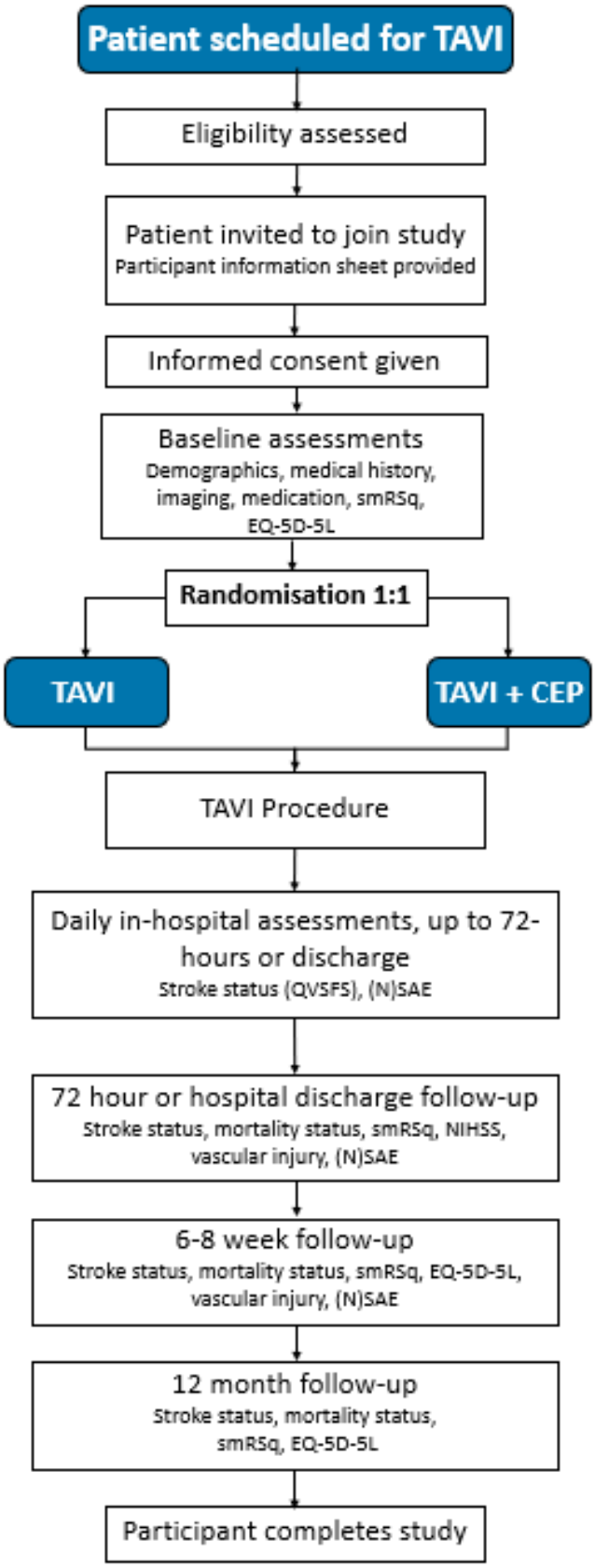
26. APPENDIX A: TRIAL FLOWCHART



27. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	04 August 2020	Alexander Perkins	- Acute Kidney injury removed as a secondary outcome - Two new secondary outcomes assessing the incidence of stroke at 30 days and then up to the end of the study to see if the device causes strokes and to identify risk factors for stroke - Inclusion criteria simplified so any patient eligible for a TAVI is approached - Randomisation process simplified to reflect the clinical use of the device - No blinding of staff as it is an open-label study - Extra assessment at 6-8 weeks follow-up for comparison of data - Patient documents updated to reflect changes to secondary outcomes and extra assessments - COVID-19 cover sheet added that can be given with PIS -No adverse event reporting at 12 months follow-up -Increase the time-period after which feasibility will be assessed from 21 months to 24 months after the trial commences - Correction of typographical errors - Addition of four new sites
2	3.0	08 February 2021	Zahra Jamal	- Serious Adverse Events reporting limited to events that are possibly, probably or unlikely related to the study treatment. Any that are definitely unrelated will not need to be reported. -Using month and year of birth and hospital number to link participants to centrally-held data -PIS updated to reflect changes to protocol -Clarified in PIS that data collected on participants who withdraw from the trial will be kept up until the point of withdrawal -Added Community Health Index as the unique identifier used in Scotland

				to link participants to their routinely collected data -Clarified the timing of randomisation in the protocol -Modified text in PIS on risk of radiation exposure to align with copy provided by Medical Physics at Sponsor - Added time of consent to the consent form - Correction of typographical errors in the protocol, PIS and consent form.
3	4.0	23/05/2022	Zahra Jamal	-Stroke severity secondary outcome added - Allow patients to be approached at participant identification centres - Option for sites to obtain consent over the telephone using the approved remote consent form -API study added (study within a trial) - Collecting participants' data of birth - Improved clarity and readability of the protocol. - Correction of typographical errors
4	5.0	14/08/2023	Zahra Jamal	-New composite secondary outcome added: Combined incidence of all-cause mortality, non-fatal stroke and transient ischaemic attack at 72 hours post-TAVI or hospital discharge (if sooner) -Transient Ischaemic Attack (TIA) definition added -Removal of MoCA collection from the trial procedures -Updates to Trial Steering Committee and Data Monitoring Committee membership
5	6.0	28/07/2024	Zahra Jamal	-Sample size increase from 7730 to 9712 participants -The duration of the study has been extended by 13 months in total; 10 month extension for the recruitment period and 3 months for the analysis. -New secondary outcome added: Incidence of all-cause mortality up to the end of the study using trial captured data up to 12 months and centrally held NHS data from 12 months up to the end of the study -New secondary outcome added: Win ratio for all-cause mortality, disabling stroke and non-disabling stroke at 72

				hours post-TAVI, or hospital discharge (if sooner) -Additional third interim analysis to be carried out once 134 events have occurred. - Newcastle upon Tyne Hospitals NHS Foundation Trust will work with LSHTM to analyse the trial data.

List details of all protocol amendments here whenever a new version of the protocol is produced.
Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, and HRA.

28. APPENDIX C: VARC-2 CRITERIA FOR VASCULAR COMPLICATIONS

Vascular Access Site and Access-Related Complications

Major vascular complications
Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR
Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
The use of unplanned endovascular or surgical intervention *associated* with death, major bleeding, visceral ischemia or neurological impairment OR
Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
Surgery for access site-related nerve injury OR
Permanent access site-related nerve injury
Minor vascular complications
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR
Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure
Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

29. APPENDIX D: PROTOCOL AUTHORS

Prof Rajesh Kharbanda, University of Oxford
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Prof James Kennedy, University of Oxford
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Prof Peter Ludman, Queen Elizabeth Hospital
Prof Daniel Blackman, Leeds General Infirmary
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Mr Richard Evans, London School of Hygiene and Tropical Medicine
Mr Alexander Perkins, London School of Hygiene and Tropical Medicine
Ms Zahra Jamal, London School of Hygiene and Tropical Medicine

30. APPENDIX E: SITE INVESTIGATORS

OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST, Rajesh Kharbanda
BARTS HEALTH NHS TRUST, Mick Ozkor
BASILDON AND THURROCK UNIVERSITY HOSPITALS NHS FOUNDATION TRUST, Rajesh Aggarwal
UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST, Stephen Dorman
UNIVERSITY HOSPITALS PLYMOUTH NHS TRUST, Venk Suresh
NHS LOTHIAN, Nick Cruden
THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST, Rajiv Das
NATIONAL WAITING TIMES CENTRE BOARD, Stuart Watkins
IMPERIAL COLLEGE HEALTHCARE NHS TRUST, Iqbal Malik
HULL AND EAST YORKSHIRE HOSPITALS NHS TRUST, Raj Chelliah
KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST, Jonathan Byrne
LEEDS TEACHING HOSPITALS NHS TRUST, Daniel Blackman
LIVERPOOL HEART AND CHEST HOSPITAL NHS FOUNDATION TRUST, Clare Appleby
MANCHESTER UNIVERSITY NHS FOUNDATION TRUST, Saqib Chowdary
SOUTH TEES HOSPITALS NHS FOUNDATION TRUST, Douglas Muir
ABERTAWE BRO MORGANNWG UNIVERSITY LHB, Dave Smith
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST, Javaid Iqbal
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UNIVERSITY HOSPITALS SUSSEX NHS FOUNDATION TRUST, David Hildick-Smith
BELFAST HEALTH AND SOCIAL CARE TRUST, Colum Owens
BLACKPOOL TEACHING HOSPITALS NHS FOUNDATION TRUST, Andrew Wiper
UNIVERSITY HOSPITAL SOUTHAMPTON NHS FOUNDATION TRUST, Nick Curzen
ST GEORGE'S UNIVERSITY HOSPITALS NHS FOUNDATION TRUST, Stephen Brecker
GUY'S AND ST THOMAS' NHS FOUNDATION TRUST, Simon Redwood
CARDIFF & VALE UNIVERSITY LHB, Richard Anderson
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THE ROYAL WOLVERHAMPTON NHS TRUST, James Cotton
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