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TITLE:

Optimum therapy for those with Atrial Fibrillation aFtEr Completing miTral valve repair surgery - The AFFECT trial

ACRONYM:

AFFECT

PROTOCOL VERSION NUMBER AND DATE:

2.0 13-NOV-2025

SPONSOR:

South Tees Hospitals NHS Foundation Trust

FUNDER:

National Institute for Health and Care Research, Health Technology Assessment Programme

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1 Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the relevant Standard Operating Procedures (SOPs), and other regulatory and governance requirements.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

The undersigned also confirm that they will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor: David Rollins	Date of signature 26-Feb-2026 | 11:41 AM GMT
Chief Investigator: Enoch Akowuah **Prof Enoch Akowuah**	Date of Signature 24-Feb-2026 | 9:42 AM EST
Study Statistician: ft• fltt>SSf>f **Helen Mossop**	Date of Signature 24-Feb-2026 | 4:57 PM GMT

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3 List of abbreviations/glossary

ACU	Academic Cardiovascular Unit (at South Tees Hospitals)
(S)AEs	(Serious) adverse event(s)
AESI	Adverse events of special interest
AF	Atrial fibrillation
(S)ARs	(Serious) adverse reaction(s)
CABG	Coronary Artery Bypass Grafting
CBA	Cost-benefit analysis
CEVR	Centre for the Evaluation of Value and Risk in Health
CEA	Cost Effectiveness Analysis
CREACs	Cost-effectiveness acceptability curves
CI	Chief Investigator
CNS	Central Nervous System
CRF(s)	Case report form(s)
CTIMP	Clinical Trial of Investigational Medicinal Product
CUA	Cost-utility analysis
CV	Curriculum vitae
DOAC	Direct oral anticoagulant
DUCkS	Data utility comparison
DVT	Deep Vein Thrombosis
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electro cardiogram
EDC	Electronic data capture (system)
ESC	European Society of Cardiology
eGFR	Estimated Glomerular Filtration Rate
GDPR	General Data Protection Regulation
GP	General Practitioner
HEAP	Health economics analysis plan
HES	Hospital Episode Statistics
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRA	Health Research Authority
HRQoL	Health-related Quality-of-Life
HRUQ	Health resource usage questionnaire
HTA	Health Technology Assessment (programme)
IDMEC	Independent data monitoring and ethics committee
INR	International normalized ratio
IRAS	Integrated Research Application System
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number (a public research registry)
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intentio n-to-treat
LAAO	Left Atrial Appendage Occlusion
MAR	Missing at random

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MCID	Minimal clinically important differences
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MR	Mitral regurgitation
MVr	Mitral Valve repair (surgery)
NCH	Net clinical harm
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR (HTA programme)	National Institute for Health and Care Research (Health Technology Assessment programme)
NIHR RON	NIHR Research Delivery Network
OAC	Oral anticoagulant
ONS	Office for National Statistics
PAG	Patient advisory group
PCI	Primary Coronary Intervention
PE	Pulmonary Embolism
PF	Physical function
PPI	Patient and public involvement
PSS	Personal social services
QALY	Quality-adjusted life years
RCT	Randomised-controlled trial
R&D	Research and Development
REC	Research ethics committee
RSI	Reference safety information
SAP	Statistical analysis plan
SCTS	Society for Cardiothoracic Surgery
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	Standard of care
SOPs	Standard operating procedures
SUSARs	Suspected unexpected serious adverse reactions
TIA	Transient Ischaemic Attack
TMF	Trial master file
TMG	Trial management group
TSC	Trial steering committee
USM	Urgent safety measure
VKA	Vitamin K antagonist
WTP	Willingness to pay

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4 Key Study Contacts

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Independent Members of the Data Monitoring and Ethics Committee	Prof. Luke Vale Prof. David Ripley Prof. Isla Mackenzie Dr. David Simcox Dr. Ines Rombach
Independent Members of the Trial Steering Committee	Mr. Nigel Drury Mr. John McAlinden Prof. Torsten Doenst Mr. Simon Kendall Dr. Puvan Tharmanathan Dr. Dwayne Boyers

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5 Study Summary

Study Title	Optimum therapy for those with Atrial Fibrillation aFtEr Completing miTral valve repair surgery - The AFFECT trial
Short Title	AFFECT Trial
Study Design	Prospective, Pragmatic, Superiority, Randomised Control Trial AFFECT will recruit 1282 patients from around 25 NHS cardiothoracic surgical centres. Further centres may be added as required.
Research Question/Aim(s)	**Main Aim:** To compare two contemporary oral anticoagulant (OAC) strategies for patients requiring anticoagulation after Mitral Valve repair surgery (MVr) using an efficient, cost-effective, inclusive trial design. **Primary Objective:** To determine the relative difference in time to all-cause mortality, major cardiovascular events or major bleeding in patients undergoing MVr for severe mitral regurgitation requiring OAC for paroxysmal, persistent or permanent atrial fibrillation treated with Vitamin K Antagonists [VKA] (e.g. warfarin) or Direct OACs (DOACs) at a minimum of 1 year post-randomisation **Primary Economic Objective:** To estimate the cost-effectiveness of DOACs in comparison to standard anticoagulant therapy based on incremental cost per quality-adjusted life year (QALY) gained at 1 year post-randomisation **Secondary Objectives,** to compare a range of patient and clinical effectiveness, safety and health economic outcomes at time-points up to 4 years post-randomisation (which is the maximum duration of follow up in the trial).
Study Participants	**Setting:** Secondary/tertiary care; approximately 25 NHS cardiothoracic surgical centres will take part. Other centres will be added as required. **Target Population:** adult patients undergoing MVr for severe mitral regurgitation with AF requiring long term anticoagulation after surgery.

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	Inclusion Criteria: • Adults aged 18 or over • Confirmed pre-op Atrial Fibrillation (AF) which should be paroxysmal, persistent or permanent • Undergone Mitral Valve repair surgery* • Require prolonged anticoagulation after MVr surgery e.g. for paroxysmal, persistent or permanent AF • Provided written informed consent **Exclusion Criteria:** • Received a mitral valve replacement or any other valve replacement. • Anticoagulation contraindicated • Already taking long term anticoagulation unrelated to an atrial arrhythmia • Antiphospholipid syndrome with triple positive antibodies • Patients who are pregnant or breastfeeding at the time eligibility is confirmed. • Patients with severe renal impairment (defined as creatinine clearance <15 ml/min) *patients undergoing concomitant Coronary Artery Bypass Grafting (CABG) and/or, tricuspid valve repair and/or left atrial appendage occlusion (LAAO) and/or Atrial Fibrillation (AF) ablation are eligible to take part.
Randomisation	Randomisation with allocation concealment will utilise a centralised, web-based system to minimise bias. Eligible participants will be assigned in a 1:1 ratio to guideline mandated therapy of a vitamin K antagonist (control) OR a Direct Oral Anticoagulant (DOAC) (intervention), stratified by persistent/permanent AF or paroxysmal AF, any intraoperative AF ablation surgery including left atrial appendage occlusion (LAAO) (received/not received), and Atrial Fibrillation related stroke risk (CHA_2DSrVA score: 0-4 or >4), and concomitant surgery (e.g. CABG, tricuspid valve repair) (received/not received)

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Trial interventions	**AFFECT will compare two strategies of care taken for the duration of the follow up period:** **Group A Intervention group (DOAC):** any DOAC **Group B Control group (VKA):** any VKA
Outcomes	**Primary Outcome:** Net Clinical Harm (NCH) defined as time to first event of all-cause mortality, major cardiovascular events (systemic thromboembolic complications/events or heart failure) or major bleeding assessed for the duration of the trial, and with a minimum follow up period of one year. **Primary Health Economic Outcome:** Incremental cost per quality-adjusted life year (QALY) gained based on responses to the EQ-5D-5L at 1 year post-randomisation. **Secondary Outcomes:** **Main secondary clinical effectiveness outcomes:** • Secondary clinical effectiveness outcome defined as a composite time to event of cardiovascular deaths and systemic thromboembolic complications/events (stroke, Transient Ischaemic Attack (TIA), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), non Central Nervous System (CNS) emboli) for the duration of the trial. • Safety outcome defined as any bleeding up to 1 year post-randomisation, and up to 4 years post randomisation. **Other clinical secondary outcomes:** • Individual components of the primary and secondary composite outcomes. • Adverse events of special interest up to 4 years post randomisation **Secondary health economic outcomes:** • Costs to NHS, patients, and lifetime cost-effectiveness • Health status (EQ-5D-5L) to four years **Other secondary outcomes:**

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	• Adherence with therapeutic strategies up to 4 years. **Long term outcomes:** Consent will be sought to follow all patients up beyond the trial, this would be subject to separate funding. A range of sub-group analyses including those to understand the impact of ethnicity, sex, and/or socio-economic status on net clinical harm, adherence to randomised strategy of OAC, and trial retention, will be detailed in the Statistical Analysis Plan (SAP).
Planned Size of Sample	**1282** randomised patients
Follow up duration	All patients will be followed for the duration of the trial, for a minimum of 1 year following randomisation up to a maximum of 4 years. Data will be collected by trial teams for the duration of the trial for all outcomes. In UK jurisdictions where Hospital Episode Statistics (HES) and Office for National Statistics (ONS) data collection is possible, this will be collected and a Data Utility Comparison (DUCkS) will be conducted to enable a comparison of concordance between HES/ONS and trial data at pre-specified time-points.
Planned Study Period	The trial length will be 68 months from 1st October 2024. Planned timelines are: • Months 1-8: protocol, REC/HRA/MHRA approval, contracting, database/randomisation system, application for HES and ONS data. • Months 9-20: internal pilot; open all 25 UK centres and recruit patients in line with pilot targets. • Months 9-47: full recruitment window • Month 59: last patient last visit. • Month 62: data lock once last patient has 1 year primary endpoint data and final data cleaning is complete. • Months 63-68: data analysis. • Months 65-68: report writing, dissemination.

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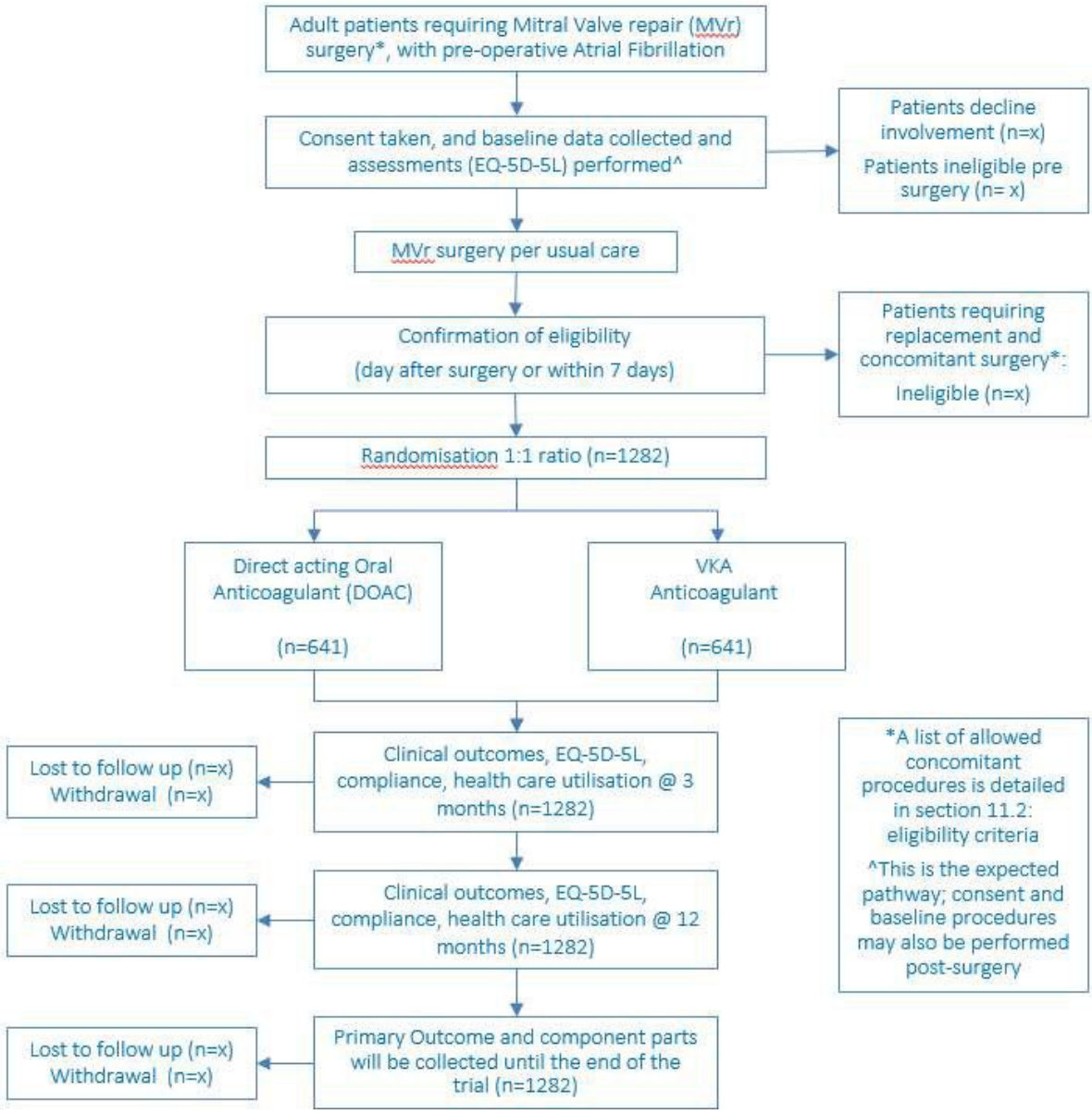
6 Trial Flow Diagram



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7 Governance

7.1 Role of the Sponsor

The Sponsor of this research in the UK is South Tees Hospitals NHS Foundation Trust; they take overall responsibility for the trial and hold the main contract for AFFECT with the Department of Health.

7.2 Role of the Funder

AFFECT has been funded in the UK by a grant from the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (NIHR160252).

The NIHR Research Delivery Network (NIHR RON) are providing additional resources at participating Trusts in the UK.

The NIHR HTA are responsible for funding the study in the UK but are not part of the day-to-day trial conduct, data analysis and interpretation, manuscript writing, or dissemination of results.

The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

7.3 Role of Trial Management Group (TMG)

The day-to-day supervision of the trial will be the responsibility of the Trial Management Group {TMG), who will report to the Trial Steering Committee. The TMG will meet regularly throughout the trial.

The TMG will consist of:

- The Chief Investigator
- Academic Cardiovascular Unit (ACU) members, including the Senior Research Manager
- Study Statistician(s)
- Health Economist(s)
- The Sponsor
- Other members of the wider co-applicant research team, including PPI co-applicants may attend TMG meetings, as required.

Responsibilities of the TMG will include, but not be limited to, obtaining and managing study approvals, site set-up and management, data quality, trial documentation and reporting obligations.

7.4 Role of the Independent Data Monitoring and Ethics Committee (IDMEC)

An Independent Data Monitoring and Ethics Committee (IDMEC)will meet at planned intervals throughout the study, and at least annually, to review data to ensure participant safety and the

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ethical trial conduct. The IDMEC will run in accordance with a trial-specific charter, which will be agreed at its first meeting. The IDMEC will consist of an independent chair, and at least two other independent members. Independence will be defined as not employed by any organisation directly involved in trial conduct.

The IDMEC will report to the Trial Steering Committee.

7.5 Role of the Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will provide overall supervision of the trial, and will monitor progress, conduct and advise on the trial. The TSC will consider the recommendations of the IDMEC, and act where required. The TSC carries the responsibility for deciding if the trial should be stopped early. Terms of reference for the TSC will be agreed at the first meeting.

The TSC will consist of voting and non-voting members. Voting members will include an independent chair, at least two other independent members and (an) independent patient representative(s). Independence will be defined as not employed by any organisation directly involved in trial conduct. The trial Chief Investigator will also be a voting member of the TSC. The TSC meetings will also incorporate non-voting members including experts from the co-applicant and collaborator teams, the CTU, the sponsor and the funder.

The TSC will meet at planned intervals, as agreed and detailed in their charter and at least annually, throughout the study and report to the Sponsor (South Tees Hospitals NHS Foundation Trust) and Funder (NIHR HTA).

8 Background

Mitral regurgitation (MR) is the most prevalent valvular heart disorder in the USA and Europe.[1,2] Untreated, severe MR has 5-year rates of death and adverse cardiac events of 22% and 33% respectively. [3,4,5,6] The gold standard treatment, mitral valve repair (MVr) surgery, is performed in over 3000 patients per year in the UK.

Post-operative thromboembolic events can complicate MVr, resulting in valve dysfunction and major cardiovascular complications.[7] The incidence of thromboembolic stroke is estimated at 2.1% at 30 days, 1.5% at 30-180 days and 0.9% per year thereafter.[8,9] Hospital Episode Statistics (HES) show these complications are 1.7 times higher in patients with atrial fibrillation (AF) after MVr.

In 2017, the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on perioperative medication in adult cardiac surgery recommended oral anticoagulation (OAC) with vitamin K antagonists (VKAs) to prevent thromboembolic events, although this recommendation was based on scant evidence. [10] The VKA most commonly used is warfarin; although effective, it has disadvantages: slow onset, narrow therapeutic window, large inter-patient variability, numerous drug/dietary interactions, and the need for regular laboratory

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monitoring through the international normalised ratio (INR) test. Even when INR levels are well controlled, warfarin and other VKAs can cause major bleeding,[11] leading to significant morbidity or death,[12] making it unattractive to patients and clinicians.

Bleeding complications from anticoagulation are devastating. In patients on OAC for AF, within 6 months of any major bleeding event, the risk of stroke, myocardial infarction, or death doubles.[13] Bleeding complications are associated with a 17% mortality and 47% rate of hospitalisation.[14] Mortality increases 8-fold after an ischemic stroke, but 27-fold after a haemorrhagic stroke.[15] A number of trials[16,17,18] demonstrate that reducing major bleeding reduces mortality.

Direct oral anticoagulants drugs (DOACs) are now widely used for non-valvular AF and have fewer stroke or systemic embolic events and importantly have lower risks of major bleeding than VKA.[19] 2024 European Society of Cardiology (ESC) Guidelines for the management of atrial fibrillation developed in collaboration with EACTS describes that patients with mitral regurgitation should be preferentially prescribed a DOAC, and the term 'valvular' should be avoided.[20] However, there is limited evidence for the use of DOACs (the most commonly used include Factor Xa inhibitors (Rivaroxaban, Apixaban and Edoxaban) and IIa inhibitors (Dabigatran)) in the prevention of thromboembolic events after MVr surgery. The more recent 2024 EACTS guidelines on perioperative medication in adult cardiac surgery observes that there is more evidence for VKA usage in this population, but DOACs seem a reasonable alternative.[21]

Despite being more expensive, DOACs are increasingly prescribed after MVr in patients who require OAC because of the perception of a lower risk of bleeding and the fact that they do not require ongoing (laboratory) monitoring.[22] For example, in a recent survey of UK surgeons, for patients with a need for OAC following MVr, 38% preferred warfarin, 37% preferred a DOAC, and 25% had no preference.[2023] Prescribing practices were similar in Danish, American and Australian surveys.[24]

DOACs andVKAs are not interchangeable in all circumstances. In patients with AF undergoing bioprosthetic mitral valve replacement, rivaroxaban (a DOAC) was non-inferior to warfarin for a primary outcome of death, major cardiovascular events, or major bleeding at 12 months.[25] Conversely in patients with rheumatic heart disease and AF, DOAC therapy led to a higher rate of cardiovascular events or death than VKA therapy.[26] There is therefore an urgent need to determine whether VKAs or DOACs are the optimum treatment to prevent thromboembolic complications whilst minimising bleeding risk in patients requiring OAC after MVr.

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9 Rationale for AFFECT

There are no randomised trials to determine the optimum anticoagulant strategy to reduce thromboembolic and vascular complications whilst minimising bleeding risk after mitral valve repair (MVr) surgery. Direct Oral Anticoagulants (DOACs) are increasingly preferred to traditional oral anticoagulation with vitamin K antagonists (VKAs e.g. warfarin) but may not be as safe in all settings. Large trials are urgently needed to inform national/international guidelines and clinical practice, which have very recently recommended the use of OACs after surgical valve repair to prevent thromboembolic events, but are unable to specify the type of OAC (Class 1 recommendation, Level of Evidence C).[21] High rates of AF related complications, and thrombogenicity of the non-endothelialised repair prosthesis and sutures are cited as the rationale for the earlier 2017 recommendations (forVKA usage),[10]but surveys of practice in the UK, and internationally, indicate that contemporary surgeon compliance with this guideline has been low, less than 50%, highlighting a knowledge gap and resulting in clinical uncertainty.[23] AFFECTwill compare contemporary anticoagulant regimes to determine the optimal therapeutic strategy following MVr using an efficient, cost effective, inclusive trial design.

10 Trial Objectives

10.1 Primary Objective

To determine the relative difference in time to all-cause mortality, major cardiovascular events or major bleeding events in patients undergoing MVr for severe mitral regurgitation and requiring OAC for long-standing paroxysmal, persistent or permanent AF, allocated to receive VKA e.g. warfarin or DOACs. Follow up will be for a minimum of 1 year post-randomisation following index MVr and a maximum of 4 years (the maximum duration of follow up in the trial).

10.2 Primary Economic Objective

To estimate the cost-effectiveness of DOACs in comparison to standard anticoagulant therapy based on incremental cost per quality-adjusted life year (QALY) gained at 1 year post-randomisation.

10.3 Secondary Objectives

To compare a range of patient and clinical effectiveness, safety and health economic outcomes at time-points up to 4 years (which is the maximum duration of follow up in the trial) that include:

- Secondary clinical outcome defined as a composite of cardiovascular deaths and systemic thromboembolic complications/events.

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- Safety outcome defined as any bleeding up to 1 year post-randomisation, and up to 4 years post randomisation.
- Individual components of the primary outcome, and secondary clinical effectiveness and safety outcomes.
- Costs to NHS, patients, and lifetime cost-effectiveness.
- Health status (EQ-5D-5L).
- Adverse events of special interest.

11 Trial Design

11.1 Summary of Participants

1282 participants with pre-existing AF and who have received a mitral valve repair operation for severe mitral regurgitation will be randomised. Participants will be randomised on a 1:1 basis to one of two anticoagulant strategies, to be taken for the duration of the follow up period:

- **Group A, Intervention group (DOAC):** any DOAC
- **Group B, Control group (VKA):** any VKA Therapy

11.2 Eligibility Criteria

11.2.1 Inclusion Criteria

1.) Adults aged 18 or over
2.) Confirmed pre-operative AF which should be paroxysmal, persistent or permanent*
3.) Undergone Mitral Valve repair surgery**
4.) Require prolonged anticoagulation after MVr surgery for paroxysmal, persistent or permanent AF
5.) Provided written informed consent

* permanent or persistent AF is defined as AF for greater than 7 days in length; paroxysmal AF may terminate spontaneously or with intervention within 7 days of onset. A single 12 lead ECG confirming the diagnosis of AF should be available (halter-monitoring over a 7 day or more period is not required). Atrial flutter is not included.

**patients undergoing concomitant Coronary Artery Bypass Grafting (CABG) and/or tricuspid valve repair and/or any AF ablation which includes left atrial appendage occlusion (LAAO) are eligible to take part; participants will be stratified at randomisation based on concomitant procedures.

11.2.2 Exclusion Criteria

1.) Received a mitral valve replacement or any other valve replacement (i.e. aortic, pulmonary or tricuspid)

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2.) Anticoagulation contraindicated
3.) Already taking long term anticoagulation unrelated to an atrial arrhythmia
4.) Antiphospholipid syndrome with triple positive antibodies
5.) Patients who are pregnant or breastfeeding at the time eligibility is confirmed
6.) Patients with severe renal impairment (creatinine clearance <15 ml/min)

11.3 Trial Setting

The trial will be conducted in approximately 25 NHS cardiothoracic surgical centres in the UK. Further centres may be added following agreement by the TMG and Sponsor.

11.4 Primary Outcome

All outcomes will all be collected from the time of randomisation. Definitions for outcomes are in section 11.6, and adverse events of special interest are in section 12.12.

Primary Clinical Effectiveness Outcome:

- Net Clinical Harm (NCH) defined as the composite time to first event of all-cause mortality, major cardiovascular events (systemic thromboembolic complications (stroke, TIA, DVT, PE, non-CNS emboli) or heart failure) or major bleeding assessed for the duration of the trial, and with a minimum follow up period of one year.

Primary Health Economic (Cost-effectiveness) Outcome:

- Incremental cost per quality-adjusted life year (QALY) gained based on responses to the EQ-5D-5L at 1 year post-randomisation.

11.5 Secondary Outcomes Measures

Main Secondary Clinical Effectiveness Outcomes:

- Secondary Clinical effectiveness outcome defined as a composite time to event of cardiovascular deaths and systemic thromboembolic events (stroke, TIA, DVT, PE, non-CNS emboli) for the duration of the trial.
- Safety outcome defined as time to any bleeding up to 1 year post randomisation following index MVr surgery, and up to 4 years post randomisation.

Other Clinical Secondary Outcomes:

- Individual components of the primary outcome and secondary composite outcomes.
- Adverse events of special interest (AESI) up to 4 years post randomisation.

Secondary Health-Economic Outcomes:

- Costs to NHS, patients, and lifetime cost-effectiveness.
- Health status at baseline, 3 months, 1 year, and annually, up to 4 years (EQ-5D-5L).

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Other Secondary Outcomes:

- Adherence with therapeutic strategies up to 4 years.

Long-Term Outcomes:

- Consent will be sought to follow all participants up beyond the trial, this would be subject to separate funding.

A range of sub-group analyses including those to understand the impact of ethnicity, sex, and/or socio-economic status on net clinical harm, adherence to randomised strategy of OAC, and trial retention, will be detailed in the Statistical Analysis Plan (SAP).

11.6 Definitions for Clinical Outcome Measures

Table 1 ***Components of the Primary Outcome***

All-Cause Mortality	Defined as any death between randomisation and the maximum follow up duration, irrespective of the cause.
Neurological Events*	**Stroke:** Defined as a non-traumatic, focal and sudden neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and is not caused by a readily identifiable cause, such as a tumour or seizure OR which resolves in <24 hours and is accompanied by clear evidence of stroke on brain imaging. Subjects who die from any cause in 30 days from the onset of a stroke due to stroke complications or without any other apparent cause will be classified as a mortality. Where advanced brain imaging studies are available, these should be analysed to help distinguish haemorrhagic stroke from ischemic stroke, and recorded as such in the case report form (CRF): • Patients with an ischaemic stroke will be included in the primary outcome as a systemic thromboembolic complication. • Patients with a haemorrhagic stroke will be included in the primary outcome under the major bleeding component and will also be included in the primary safety analysis.

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	• Patients where no imaging is available and the type of stroke is unknown will be included in the primary outcome as a systemic thromboembolic complication. **Transient Ischemic Attack:** Defined as a neurological focal deficit lasting <24 hours and not due to an identifiable non-vascular cause (example: brain tumour, trauma), AND absence of new stroke on brain imaging (if available).
Non-CNS emboli*	Systemic embolism without central nervous system (CNS) involvement is defined as an abrupt vascular failure associated with clinical and radiological evidence of arterial occlusion without other likely mechanisms (eg trauma, atherosclerosis or instrumentation). In the presence of a history of atherosclerotic peripheral arterial disease, the diagnosis of embolism in the lower limbs requires an angiographic demonstration of abrupt arterial occlusion.
Venous thromboembolic events*	**Pulmonary Embolism:** As determined by: • A defect in intraluminal filling in segmental or more proximal branches of spiral computed tomography; an intraluminal filling defect or an extension of an existing defect or sudden cut-off point of vessels greater than 2.5 mm in diameter on pulmonary angiography. • High probability of ventilation-perfusion defect on pulmonary scintigraphy. • Findings at autopsy. **Deep Vein Thrombosis:** As determined by: • An abnormal compression ultrasound (USC); • A defect of intraluminal filling in venography; • During an autopsy.

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Heart Failure*	Hospitalisation for heart failure is defined as an outcome if documented with an admission report or hospital admission form that considers decompensated heart failure of any functional class or status and that justifies the participant's hospitalisation with a hospital stay of more than 24 hours. The date of the event will be the date of admission.
Major Bleeding	Classified according to the ISTH (International Society on Thrombosis and Haemostasis) definition, major bleeding will be any bleeding that fulfils **at least one** of the following: 1. fatal bleeding (This will then be classified as mortality for inclusion in the primary analysis under all-cause mortality; included as part of the secondary analysis if it is considered a cardiovascular mortality; and included in the safety outcome as a bleed); 2. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardia!, or intramuscular with compartment syndrome; 3. bleeding causing a fall in haemoglobin levels of 1.24 mmoVL (20 g/L or greater) or more, or leading to a transfusion of 2 U or more of whole blood or red cells.

Additional Components for Secondary Outcomes

Non-Major Bleeding	**Clinically Relevant Non-major Bleeding**:** Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: 1. requiring medical intervention by a healthcare professional 2. leading to hospitalisation or increased level of care 3. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation **Other Bleeding:**

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	Other bleeding will be all bleeding reported by participants that cannot be classified as major according to the ISTH definition or clinically relevant non-major bleeding as defined above.
Cardiovascular Mortality*	All deaths will be assessed as having cardiovascular causes (e.g., stroke, embolism or acute myocardial infarction) or non-vascular causes due to conditions such as malignancy or haemorrhage. The outcome will be adjudicated when collected within trial.
**adapted from the endpoint definitions in:* *[25]Guimaraes HP, Lopes RD, de Barros e Silva PGM, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med 2020;383:2117-26. DOI: 10.1056/NEJMoa2029603* ** *[27]Kaatz* S, *Ahmad D, Spyropoulos AC, Schulman* S, *for the Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the* SSC *of the ISTH. J Thromb Haemost 2015; 13: 2119-26.*	

11.7 Adjudication of Outcomes

An independent adjudication panel will be convened to adjudicate all the components of the primary outcome and cardiovascular mortality collected as part of the within trial data collection. The panel will be blinded to treatment allocation.

12 Trial Procedures

12.1 Schedule of Events/Data Collection

Assessment	Baseline (expected to occur pre-surgery)	Surgery	Post-Operative (pre-discharge or within 7 days post-index MVr surgery, whichever is earlier)	Pre-discharge	3 Months following randomisation (+/-2 weeks)	1 year following randomisation (+/-4 weeks)	Annual Follow up beyond 1 year following randomisation (+/- 4 weeks)
Informed Consent	X						
Demographics, Height and Weight	X*						
Medical/Cardiac History (including degree of MR by TTE)	X*						
Concomitant medications	X*				X	X	X
Questionnaires: EQ-5D-5L	X*				X	X	X
Health Resource Usage questionnaire	X*				X	X	X
Procedure details (including degree of MR by TTE)		X					
CHA_2DS_2-VASc and CHA_2DS_2-VAscores		X**					
HASSLED score		X**					
ORBIT Score		X**					
EUROSCORE2		X**					
Eligibility Check			X				
Randomisation			X				
OAC started based on randomised allocation				X			
Clinical Events -AESI, NCH, Other outcomes			X		X	X	X
Adherence with randomised strategy (DOAC v VKA)					X	X	X
Time and Travel questionnaire						X	
HES/ONS data collection			X		X	X	X

*baseline assessments should be undertaken within 6 months prior to randomisation.
**these scores should be calculated using contemporary data at the time of index surgery, and prior to randomisation.

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12.2 Identification of Participants

Potentially eligible participants will be identified from outpatient clinics at participating hospitals when surgery is scheduled, and/or in hospital whilst patients are awaiting MVr surgery, or have had MVr surgery during their index hospital admission. The majority of participants are expected to be identified as their surgery is scheduled and will be invited to take part in preoperative clinics, but patients can also be recruited if identified during their index hospital stay.

12.3 Informed Consent

Eligible patients will be sent, be able to download from a website, or, given a participant information sheet describing the study and will be able to speak to a member of the research team about the trial. Where pre-surgical assessment consultations occur via remote means (e.g., video call); patients may also be approached about the trial during this remote consultation. Conversations with patients about the trial should be documented in the patient notes.

Once the clinician/research team has discussed the trial with the patient and after opportunity for questions, a delegated and trained member of the research team will seek consent.

Patients who agree to participate will sign a consent form, which in most cases will be prior to surgery. As the pre-surgical assessment may be a remote consultation, consent may be achieved remotely. The provision of written consent includes via electronic methods. Electronic signatures may include signatures that are scanned, an electronic representation of a handwritten signature, or the use of simple electronic signature systems.Remote consent may also be obtained by return of the consent form with a wet-ink signature. Counter-signature will be provided by the trained and delegated member of the research team seeking consent. Where the consent is provided remotely (e.g. is a wet-ink signature on a posted consent form), the counter signature by the research team member may be on a later date to the participant's dated signature. A copy of the consent form will be returned to the participant in person, by post or electronically. The methods used at individual sites will need to comply with local policies for remote consent, and be approved by the Sponsor.

Translations of the information sheets and consent forms will also be available. The Clinical Trials Unit will work with sites and various stakeholders to confirm the number of appropriate languages for translations and distribute these to sites once approved for use.

12.4 Confirmation of Eligibility

A suitably qualified member of the clinical research team on the delegation log will confirm the participant's eligibility prior to randomisation by reviewing the full eligibility criteria, finalising

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completion of the eligibility proforma/CRF, and documenting confirmation of eligibility in the medical notes; it is expected that eligibility will be predominantly established pre-surgery, with final confirmation only possible once a successful MVr is performed.

Final eligibility will only be confirmed after the completed signing of a consent form, and post operatively to ensure the planned MVr procedure was performed, after which the participant can be randomised if fully eligible.

Eligibility should be confirmed post-operatively, within 7 days of index surgery or prior to discharge, whichever is earlier.

Participants can be randomised following confirmation of eligibility (also up to a maximum of 7 days following index surgery, or prior to discharge, whichever is earlier).

12.5 Screening Log and Screen Failures

All potentially eligible patients should have their details added to the electronic screening log, This will include those referred to the unit in need of, or having had, mitral valve repair surgery for mitral regurgitation with concomitant AF.

Those patients who provide consent but who are not subsequently found to be eligible will be considered a screen fail. Those that decline participation should be asked why, and their reason recorded on the log where this is given.

The screening log will contain details of the following for every patient screened by the trial team about the trial:

- Age
- Year of birth
- Sex at birth
- Ethnicity
- Postcode
- Reason the patient did not take part or was ineligible, if applicable and available
- Consent details

Redacted screening logs (with personal identifiers other than those listed above removed (e.g., name, NHS numbers (or equivalent), contact details etc), should be sent to the Clinical Trials Unit monthly for monitoring purposes.

12.6 Participant ID

Each participant will be given a unique study ID number at the point of consent. This study ID number will be used to identify the individual participant throughout the study and will not be re-assigned to any other participant.

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12.7 Randomisation

For consenting patients, randomisation can only occur following confirmation of eligibility post-operatively. Randomisation will be undertaken by delegated members of the clinical research team using a validated web-based system (CASTOR). The randomisation system will use permuted random blocks of variable length, block sizes are not disclosed here to ensure allocation is not predictable. Eligible and consenting participants will be randomly assigned in a 1:1 ratio to one of two arms:

GROUP A (intervention): Allocated to a strategy of any Direct Oral Anticoagulant (DOAC)
OR
GROUP B (control): Allocated to a strategy of any Vitamin K Antagonist (VKA)

Randomisation will be stratified by:

- Type of AF (paroxysmal or permanent/persistent)
- Any AF Ablation surgery including LAAO (received/not received),
- AF related stroke risk (CHA_2DSrVA score) (0-4 or >4)
- Concomitant surgery (e.g. CABG or TVR) (received/not received)

Once randomised, the participant should be prescribed the allocated anticoagulant, which should be started before discharge.

12.8 Blinding

Study participants, clinicians and the ACU team will be aware of treatment allocation. The Statistical Analysis Plan (SAP) will be developed by statisticians who are unaware of treatment allocation and will be finalised and signed-off prior to unblinded data being reviewed by the IDMEC. The SAP will contain full details of the final analyses, with details of who will perform these analyses. Some statisticians may have access to unblinded data for the purposes of creating IDMEC reports. During the trial, only the unblinded statisticians will have access to the closed IDMEC reports, unless the IDMEC request that unblinded comparative information is released. In the case that a major amendment is proposed to the SAP, this will be approved by an appropriate blinded statistician.

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12.9 Informing General Practitioners of Trial Participation

General Practitioners (GPs) will be informed of their patient's decision to participate once patients have consented to this. A letter providing information about the study, requesting that patients remain on their allocated OAC for the duration of the trial, and inviting GPs to contact the investigators, if they have questions, will be sent following randomisation. A follow-up GP letter will be sent at the end of the follow up period confirming that the patient is no longer part of the trial.

12.10 Assessments

12.10.1 Questionnaires

Participants can choose to complete the questionnaires:

- On paper, with data entered onto the database by the research team at individual sites.
- Via direct data entry to the on-line database by the participant. Participants must provide a personal email address for the CASTOR system and an electronic link will be sent to them at the required times.
- Via direct data entry to the on-line database by the research team if administration is over the phone with the participant, or in person.

Questionnaires to be completed are:

- Outcomes questionnaire (this will help act as a prompt for when the trial teams call participants for their scheduled trial visits which will be at 3 months, 1 year and annually after randomisation).
- EQ-5D-5L will measure health related quality of life.
- A bespoke Health Resource Usage questionnaire (HRUQ) will collect data on health care visits. This will be developed from those used in previous studies and relate to services potentially used by participants.
- An adherence questionnaire will collect data on adherence to the randomised strategy, which will include INR values for those receiving warfarin.
- A time and travel questionnaire.

Questionnaires will be completed at the following time-points:

- Baseline (EQ-5D-5L and HRUQ only)
- 3 months following randomisation (Outcomes, EQ-50-5L, HRUQ and adherence)
- 1 year following randomisation (Outcomes, EQ-5D-5L, HRUQ, time and travel, and adherence)
- Annually thereafter (Outcomes, EQ-50-5L, HRUQ, adherence)

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- 3 monthly (Outcomes and adherence will be administered online (for those participants that provide an email address) at 6 and 9 months after randomisation and then three monthly after the 1 year visit).

12.10.2 Medical History

A full medical history will be recorded for each participant at baseline and will include details of their mitral valve disease, all clinically significant past cardiovascular medical conditions and all clinically significant on-going cardiovascular or other medical conditions. Review of other hospital notes (and requests to access information in GP notes) may be required to complete the medical history.

12.10.3 Concomitant Medications

A list of selected medications currently taken by the participant, will be recorded at baseline, 1 year, and annually.

12.10.4 Demographic

Demographic details including height and weight at baseline will be recorded from the pre-operative measures in medical notes.

12.10.5 EuroSCORE II

EuroSCORE II and its constituent parts should be recorded by the clinical team as part of routine care at the time of surgery. Full details will be added to the trial database.
https://www.euroscore.org/index.php?id=17

12.10.6 CHA_2DSz-VA score

The CHA_2DSz-VA calculates stroke risk in patients with AF.[28] It should be calculated at baseline, with full details required in the trial database. The final score will also be required for the randomisation system and can be found in Table 10 of the ESC guidelines accessible using the following link:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation

12.10.7 CHA_2DSz-VASc score

The CHA_2DSz-VASc calculates stroke risk in patients with AF.[29] It should be calculated at baseline, with full details required in the trial database.
CHA_2DSz-VASc Score for Atrial Fibrillation Stroke Risk (mdcalc.com)

12.10.8 HASSLED Score

The HASSLED score estimates the risk of major bleeding for patients on anticoagulation to help assess risk-benefit in AF care.[30] It should be calculated at baseline, with full details added to the trial database.
HAS-BLED Score for Major Bleeding Risk (mdcalc.com)

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12.10.9 ORBIT Score

The ORBIT bleeding risk score in AF is used to predict bleeding risk in patients on anti-coagulation for AF.[31] It should be calculated at baseline, with full details added to the trial database.

ORBIT Bleeding Risk Score for Atrial Fibrillation (mdcalc.com)

12.11 Trial Interventions

The AFFECT trial will compare two OAC strategies, with treatment continuing for the duration of the follow up period and to a minimum of one year following randomisation:

GROUP A (intervention):	Allocated to a strategy of any Direct Oral Anticoagulant (DOAC)
	OR
GROUP B (control):	Allocated to a strategy of any Vitamin K Antagonist (VKA)

This is a pragmatic strategy trial. The trial team will not provide any medication and medication should be provided from hospital stocks initially and thereafter via repeat prescriptions issued by General Practitioners (GPs) as per routine care. Storage and handling of medications should be in accordance with the manufacturers' instructions; there are no study-specific labelling or handling instructions.

The choice to prescribe any licenced DOAC (for participants randomised to the DOAC arm) or VKA (for participants randomised to the VKA arm) will be at the Investigator's discretion. Dosing, including dose reductions should be in accordancewith unit practice, routine standard care and international guidelines for the management of AF. The choice of therapy should take into consideration a participant's renal and hepatic function, concomitant medications and contraindications as outlined in the summary of product characteristics (SmPCs). The name of the prescribed medication will be entered into the database. GP letters will include information about the trial and a requirement for participants to be maintained on their randomised trial treatment for the duration of the follow up period. An assessment of adherence to randomised medication will be made at 3 months and 1 year, and annually thereafter.

The participant should begin taking the OAC strategy to which randomised prior to discharge. The exact timing of starting the drug within this period will be at the discretion of the clinical team.

AFFECT is a Clinical Trial of an Investigational Medicinal Product (CTIMP). In the UK it is conducted in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, and the approved protocol.

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In the event that complications occur requiring the patient to change to an alternative treatment, this should be reported to the trial team and recorded in the CRF.

12.11.1 Switching between DOACs in the DOAC Arm

Participants randomised to DOAC may switch between different DOACs at the discretion of the prescribing clinical team as long as they are maintained within their randomised strategy. There should not be any interruptions in DOAC treatment unless clinically indicated.

12.11.2 VKA

VKAs should be given in accordance with unit practice. Most participants are expected to be prescribed warfarin and INR targets, frequency of monitoring and dose adjustments will be at the discretion of the prescribing clinical team and according to standard procedures. Dose adjustment is expected to occur with a measurement of the INR obtained regularly in order to maintain the INR in the therapeutic range (usually 2.0 to 3.0). There should not be any interruptions in VKA treatment unless clinically indicated. INR results will be recorded on the patient completed adherence questionnaire at month 3 and month 12, and annually thereafter for patients randomised to the VKA arm and who receive warfarin; INR diaries provided as part of usual care will assist in providing this information. This will allow the trial team to calculate the Time in Therapeutic Range using the Rosendaal method.[32]

Use of INR Self-Monitoring Devices:

The requirement for frequent testing is known to be a barrier to some participants agreeing to take VKAs (and consequently to participate in the trial). This may be due to carer support, timings of INR clinics, transport (including costs of travel), time and distance to travel to the anticoagulant clinic. Therefore, the use of INR self-monitoring devices will be permitted in this trial. In some regions INR self-testing devices may be offered as part of routine care. Some participants may already have an INR self-testing device of their own, and participants may be provided with commercially-available INR point-of-care self-monitoring devices by the study team. The decision to offer the device to participants randomised to receive VKA will be at the discretion of the Principal Investigator. Participants who are offered a device to use will receive training on correct operation and recording of readings. Devices will be used with the knowledge and oversight of the participant's primary care provider or anticoagulation clinic, and test strips will be supplied through routine care. The dosing and re-testing requirements will remain with the participant's primary care provider or anticoagulation clinic, as per usual care.

12.11.3 Crossovers

Crossovers are not permitted in the trial unless clinically indicated. An adherence questionnaire will be administered at 3 months and 1 year to confirm that participants remain

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within their randomised strategy, and to record those that have discontinued their randomised medications and why. Rates and data on adherence will be regularly reviewed during the course of the trial.

12.11.4 Discontinuation

In the event that a participant stops treatment, this should be recorded as a discontinuation in the CRF. Where an adverse event resulted in the discontinuation of treatment, this should also be recorded in the CRF as appropriate. This is an intention to treat trial and patients should continue to be followed irrespective of drug changes or discontinuation of randomised strategy, i.e., discontinuation is not the equivalent of withdrawal from the trial.

12.12 Follow-up

Participants will be followed up by trial teams at 3 months and 1 year, and annually thereafter following randomisation until the end of the follow up period. Research visits are expected to be over the telephone at these time-points, though some patients may request that they visit hospital (see section 20 for remuneration of patient travel). The three monthly outcomes and adherence questionnaires send through the CASTOR system are intended to act as prompts for the research team and to maintain engagement in the trial. In the event that participants are unable to be contacted by telephone, data from these may be used in the trial.

Follow up will require research teams to collect data from participants and from review of their medical notes, including contacting GPs where needed to gather information on events occurring at other hospitals on **all outcomes as detailed in section 11.6, and additionally the following complications/Adverse Events of interest:**

- Requirement for any blood (whole blood or red cell) transfusion following index surgery following randomisation
- Any Adverse Events resulting in treatment discontinuation
- Any requirement for revascularisation (percutaneous coronary intervention (PCI), CABG)
- Any non-procedural Myocardial Infarction
- Any non-cardiac vascular surgery
- Any further cardiac interventions (including valve re-interventions)
- Any major vascular complication following procedure
- Any reoperation for postoperative bleeding
- Endocarditis
- Mitral valve failure
- Acute Kidney Injury (Stage 2 or 3)/Renal failure (creatinine clearance <15 ml/min)
- Pleural effusions requiring drainage or surgery

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- Pericardia! effusion requiring drainage or surgery
- Wound dehiscence
- Wound infection
- Wound haematomas

Participants who provide a personal email address to complete questionnaires using the CASTOR system, will also be sent alerts through CASTOR every 3 months from the time of randomisation to remind them to contact the study team if they have any complications, and to keep them engaged between the trial visits. This will include a brief questionnaire of outcomes of interest to help with data collection at the 3 month, 1 year and annual trial visits.

12.13 Safety Reporting Definitions

Adverse Events (AEs) are defined as any new medical occurrence, or a worsening of a pre-existing medical condition in a participant that has received a study intervention, or undergone procedures required by the study, which does not necessarily have to have a causal relationship to the study intervention or its procedures.

Adverse Reactions (ARs) are defined as any new medical occurrence, or a worsening of a pre-existing medical condition in a participant that has received a study intervention, which is considered related to the medicinal product. They can be expected or unexpected when checked against the Reference Safety Information (RSI) for the medicinal product.

Serious Adverse Events (SAEs) are defined as any adverse event which:

- results in death;
- is life-threatening;
- requires hospitalisation, or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

Serious Adverse Reactions (SARs) are SAEs that are related to the medicinal product and are expected in accordance with the RSI for the medicinal product.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are related to the medicinal product but unexpected in accordance with the RSI for the medicinal product.

Outcomes and Adverse Events of Special Interest (AESIs) are detailed in section 11.6 and 12.12.

Reporting requirements for all Adverse Events are given in Figure 1 and 12.13.1, and an alternative representation of this may be found in the Appendix.

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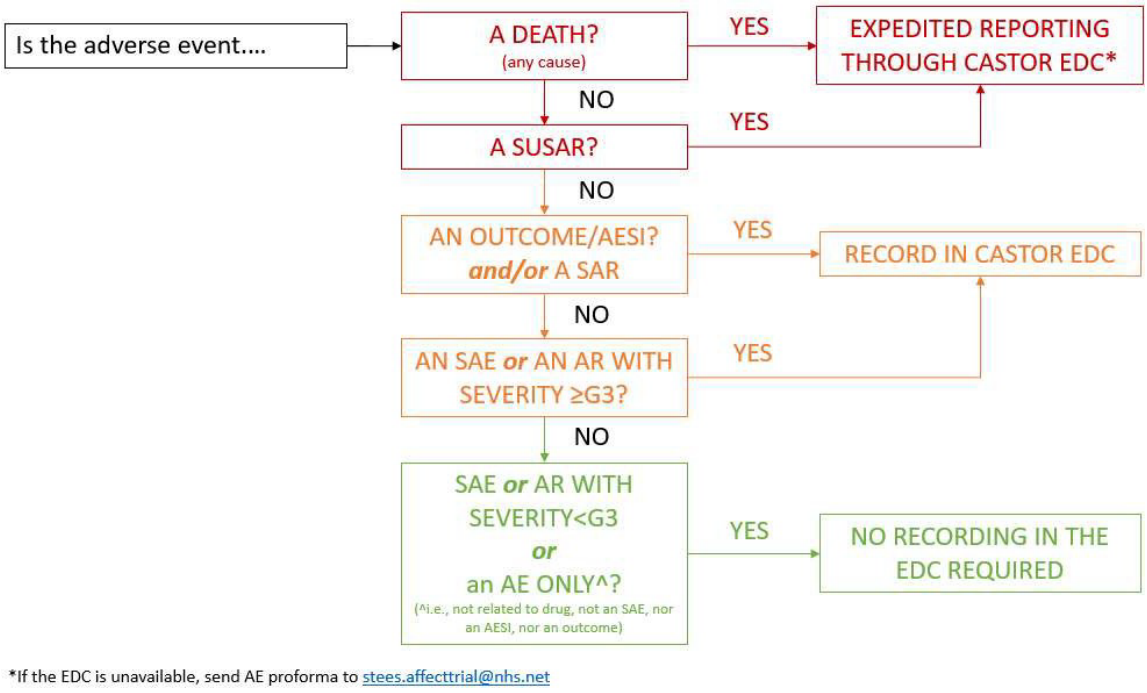

Figure 1: Adverse Event reporting requirements, see section 12.13.3 and 12.13.4 below for severity and causality scales

12.13.1 Event Reporting including expedited reporting

All events and outcomes will be recorded from the point of randomisation. For all events, Principal Investigators/delegated sub-Investigators will perform an assessment of severity (see Table 2), and causality {Table 3) in relation to the intervention (DOAC or VKA). Where an event is considered possibly, probably or definitely related to the DOAC or VKA and it is SAE it should be assessed against the RSI to determine if it is a SAR or a SUSAR. SUSARs/potential SUSARs require expedited reporting to the ACU within 24 hours of the research team becoming aware of the event. Where the AE is bleeding, the assessment of bleeding severity should be against **both** the bleeding definitions in Table 1 and the BARC definitions in Table 4 .

The ACU will perform expedited reporting to the Research Ethics Committee (REC) and Medicines for Health Care Products Regulatory Agency (MHRA). This reporting will be Urgent Safety Measures (USM) and SUSARs.

For all reporting, including expedited reporting from site to the ACU, the primary mechanism will be the EDC.The appropriate case report forms (CRFs)should be completed with the initial information within 24 hours of awareness of a SUSAR. If the EDC is unavailable, the initial report may be provided via an Adverse Events proforma (a template form is available in the study document pack), sent by email within 24 hours of awareness of the event to:

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stees.affecttrial@nhs.net. The email should be followed with data entry into the EDC as soon as it is feasible. The ACU will undertake an additional assessment against the RSI for all SUSARs and SARs.

12.13.2 Outcomes or Adverse Events of Special Interest (AESIs)

Outcomes and Adverse Events of Special Interest (AESIs) in this study are listed in section 11.6 and 12.12. All Outcomes and AESIs will be recorded in participant medical notes and the EDC system up to four years following randomisation, or until withdrawal where this is earlier.

12.13.3 Severity Assessment

Table 2

Grade 1	Minor adverse event, not requiring medical intervention. May be asymptomatic and is likely to be a clinical or diagnostic observation only; or may be a symptomatic but minor, or transient event, with no necessity for medical intervention. This might include asymptomatic laboratory or radiographic findings. A minor adverse event is likely to have only marginal clinical relevance.
Grade 2	An adverse event which may require some medical intervention (local/non-invasive) and which is symptomatic to patient. May affect activities of daily living.
Grade 3	Significant symptoms reported, requiring medical intervention and possibly requiring hospitalisation. Medically significant and likely to be significantly affecting activities of daily living.
Grade 4	An adverse event that requires urgent intervention or may have life threatening consequences
Grade 5	Death related to the adverse event

12.13.4 Causality Assessment

Table 3

Unrelated	The event is not considered to be related to the drug.
Unlikely to be related	The event is considered unlikely to be related to drug; there is little evidence to suggest a causal relationship or there is another reasonable explanation for the event.
Possibly related	Although the relationship to the drug cannot be ruled out, the nature of the event, the underlying disease, concomitant medications or temporal relationship make other explanations plausible.
Probably related	The temporal relationship and an absence of a more likely explanation suggest that drug is the most likely cause.
Definitely related	The known effects of the drug indicate this to be the most likely cause and other contributing factors can be ruled out.

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12.13.5 Bleeding Academic Research Consortium (BARC) Classification System

Table 4

BARC Definitions	Type 1: Bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.
	Type 2: Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, type 4, or type 5 but does meet at least one of the following criteria: requiring nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation.
	Type 3a: overt bleeding plus a haemoglobin drop of 3 to 5 g/dl* (provided the haemoglobin drop is related to bleed); any transfusion with overt bleeding. Type 3b: overt bleeding plus a haemoglobin drop of 5 g/dl (provided the haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and haemorrhoid); bleeding requiring intravenous vasoactive agents. Type 3c: intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging, or lumbar puncture; intraocular bleed compromising vision.
	Type 4: Coronary artery bypass grafting-related bleeding; perioperative intracranial bleeding within 48 hours; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U of whole blood or packed red blood cells within a 48-hour period; chest tube output 2 L within a 24-hour period.
	Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious. Type 5b: definite fatal bleeding; overt bleeding or autopsy, or imaging confirmation.

12.13.6 Pregnancy Reporting

Pregnancy should be reported as soon as it is known (within 24 hrs of site awareness) using the appropriate pregnancy reporting form. Pregnancies should be followed to determine the outcome.

Participants who become pregnant should remain in study for follow up purposes as this in an intention-to-treat trial. The decision regarding continuation of their randomised anticoagulation

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regime will be at the participant's clinical team discretion, with any changes or discontinuation recorded.

12.14 Participant Withdrawal

Participants may withdraw from the study at any time if they wish to, without giving reason and without any adverse consequences to their continued treatment. This decision should be recorded in the participant's medical notes. Data collected up to the point of withdrawal from the study as a whole will be retained.

If a participant signals their intention to withdraw, they should be asked if they only wish to withdraw from certain elements of the trial, such as completion of EQ-5D-5L questionnaires. Analysis will be on an intention to treat basis. The Trials office should be contacted immediately if a participant expresses an intention to withdraw from the study. If a participant does progress to full withdrawal, it should be established at this point if this includes withdrawal from being followed up using routine data sources (medical notes, HES/ONS or equivalents).

All participants will be made aware of their right to withdraw from the study, and this information will be included in the participant information sheet.

13 Statistics

13.1 Sample Size

A sample size of 1282 participants (641 per arm), using all events from follow-up, would allow us to detect a Hazard Ratio (HR) of 0.679 (equivalent to a 30% reduction in the event rate at one year, from 18% to 12.6%) with 90% power and 5% two-sided type I error rate.

This calculation was performed using the 'artsurv' command in Stata software and is based on the following assumptions:

- The NCH event rate is 18%, 25%, 31%, 36% and 41% at one, two, three, four and five years respectively in the control arm. These figures were based on NHS HES data (including 10,223 patients undergoing MVr between 2012-2018, 6342 with AF, with follow-up until March 2020)
- 10% of patients are lost to follow-up by 1 year

Recruitment will be staggered with 4% of the total sample size recruited within months 1-6, 12% within months 7-12, and constant recruitment rates for the remaining recruitment period.

These assumptions will be monitored by the IDMEC during the conduct of the trial.

The target effect size was supported by PPI engagement and by clinicians and trialists as part of The British Heart Foundation Clinical Research Collaborative.

13.2 Statistical Analyses

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Full details of all statistical analyses will be provided in a statistical analysis plan (SAP) which will be developed and agreed prior to the first data monitoring report where comparative outcome data is presented.

The primary analysis will be conducted in the intention-to-treat population, to evaluate a treatment policy estimand. A Cox regression model will be used to estimate the hazard ratio of intervention to control for time to first event over the full duration of follow-up, adjusting for variables used to stratify the randomisation. If the proportional hazards assumption is not found to hold we will use alternative approaches as appropriate for the pattern/type of non-proportional hazards, such as an accelerated failure time model and/or calculation of the restricted mean survival time.

We will also fit logistic regression models to the NCH rate at three months and one year, adjusted for stratification variables.

We will supplement the analysis of the composite primary endpoint by 1) analysing individual components of NCH separately; 2) using the Wei-Lachin test[33] to combine intervention effects for each type of event into one test statistic. This test uses the estimated between-arm differences for each component and calculates the sum of these differences across all components; 3) using the Win-Ratio method[34] which gives greater weighting to more clinical important events (e.g. mortality).

Secondary endpoints will be analysed using appropriate regression models, depending on the endpoint type. Time to event outcomes will be analysed as described for the primary outcome, with competing risks analyses also performed where appropriate. Recurrent events will be reported and analysed using appropriate event count regression models, such as the negative binomial model.

Treatment adherence will be summarised descriptively in each randomised treatment group.

Adverse events will be summarised by study arm. For each AESI, event rates will be estimated and reported with 95% confidence intervals. Risk differences between treatment groups will also be reported.

Subgroup analyses for the primary outcome will be carried out in pre-defined subgroups of interest, including ethnicity, sex, and/or socio-economic status.A full list of subgroup analyses will be provided in the SAP.

No formal interim analyses are planned; comparative data may be presented to the IDMEC as requested by them.

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14 Health Economics

14.1 Economic Analyses

The economic evaluation will include (1) a within trial analysis in the form of a cost utility analysis based on incremental cost per QALY gained at 12 months, using responses from the EQ-5D-5L and (2) a longer-term model extrapolating costs and outcomes over a lifetime time horizon.

Within Trial Analysis

Estimation of Costs: All relevant costs from an NHS and Personal & Social Services (PSS) perspective associated with treatment and subsequent management (including complications) will be measured. Data from the trial will estimate the cost of the interventions. Subsequent use of health services will be captured via a health resource utilisation questionnaire (HRUQ) administered at baseline, 3 and 12 months and annually post-randomisation. A broader perspective will include costs borne by participants (e.g. time off work or usual activities, out of pocket purchased health care), elicited from the HRUQ and from data from a time and travel questionnaire which will be used to estimate the time and travel costs of accessing care. The timing of this questionnaire will be set to minimise respondent burden.

Unit costs will be derived using routine data sources and study specific estimates. Data on the cost of the intervention and subsequent use of services will be combined with unit costs to produce a cost for each trial participant. Mean costs per intervention from an NHS perspective will be subsequently calculated. A mean cost, taking into account patient costs will likewise be estimated.

Estimation of QALYS: Changes in health-related quality of life will be measured via responses to the EQ-5D-5L following guidelines for best practice. [35] EQ-5D-5L will be collected at baseline, 3 and 12 months. Responses will be combined with a UK tariff that is recommended at the time of the analysis and used to estimate QALYs.

Estimation of cost-effectiveness: Point estimates of mean incremental costs and QALYs will be presented. For the primary economic analyses no discounting of costs and QALYs will be performed.

An adjusted analysis will estimate point estimates of mean incremental costs, effects and cost-effectiveness using seemingly unrelated regression (SUR), accounting for baseline costs and QALYs.[36] The results will be presented as point estimates of costs, QALYs and cost-effectiveness. Cost and QALYs will also be reported with 95% confidence intervals as well as cost and QALY plots. To display the statistical imprecision in estimates of cost-effectiveness we will use stochastic sensitivity analysis to produce cost-effectiveness acceptability curves

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(CEACs) to show whether interventions are cost-effective at different threshold values for society's willingness to pay for a QALY.

Sensitivity analysis: In addition to statistical imprecision in estimates of cost-effectiveness, the results will be subject to other forms of uncertainty e.g. perspective NHS vs NHS plus patient; derivation of unit costs, etc. To address these forms of uncertainty deterministic sensitivity analyses will be used. This will be displayed both deterministically e.g. in Tornado diagrams, and combined with the stochastic sensitivity analysis and reported as both cost and QALY plots and CEACs.

Missing Data: It is expected that not all participants who enter the study will complete all questionnaires and/or all of the questions in each questionnaire, therefore missing data is expected. We will explore the nature and pattern of missing data and choose appropriate methods to handle this. It is likely, if data are missing at random, that chained multiple imputation methods will be used but additional sensitivity analysis exploring the impact of alternative methods will be undertaken. [37]

Longer term model: A serious complication of MVr is post-operative thromboembolic events, resulting in valve dysfunction and major cardiovascular complications including elevated risk of ischaemic and thromboembolic stroke that persists beyond the trial follow-up. (12) Therefore, the time horizon adopted within the within trial analysis (12 months) may not capture all costs and outcomes associated with each of the interventions. We propose to develop an economic decision model to extrapolate from the short-term trial findings over the patient lifetime. The structure of the model will be informed by previous models conducted in this area and co-designed with stakeholders - especially those who have received MVr, to ensure that the model reflects their lived experience and medically and non-medically qualified clinicians involved in the provision of care.

The model will be developed in accordance with NICE reference case[38] and guidelines for good practice.[39] We anticipate that in order to make the best use of the trial data an individual patient level simulation model will be used. However, the use of other frameworks will be explored to ensure that we can best address the decision question with the data available.

Trial data, including HES and ONS data (or equivalents) will be the main source of data to populate the models with further data derived systematically from relevant literature and clinical input. Our initial scoping work suggests that it is feasible to assemble relevant data.

The results of the longer-term analyses will be presented as point estimates of mean incremental costs, QALYs and incremental cost-effectiveness ratios. We anticipate also producing a range of model outputs e.g. predictions of life years, incidence of clinical events like stroke etc. This will serve multiple purposes. First it will allow metrics to consider model

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validity against both clinical and patient experience as well as external data sources and second it will provide further information to aid in interpretation of cost and QALY findings.

For all economic analyses, deterministic sensitivity analysis will explore key uncertainties (e.g. impact of alternative care pathways, alternative input parameters, etc). Where appropriate this will be combined with probabilistic sensitivity analysis with results presented as point estimates, cost and QALY plots and CEAC.

15 Trial Timelines

The trial length is anticipated to be 68 months from 1st October 2024.
Planned timelines are:

- Months 1-8: protocol, REC/HRA/MHRAapproval, contracting, database/randomisation system, HES/ONE application.
- Months 9-20: open all UK centres
- Months 9-20: internal pilot
- Months 9-47: recruitment
- Month 59: last patient last visit.
- Months 60-62: final data cleaning, data lock
- Months 63-65: data analysis.
- Months 66-68: report writing, dissemination.

16 Internal Pilot

Key assumptions about recruitment and processes will be tested in a 12-month internal pilot running from month 9 (projected start of recruitment) to month 20 with pre-specified progression criteria.

The internal pilot will aim to confirm the feasibility of anticipated recruitment rates. During the pilot we will monitor recruitment and retention at each centre and investigate processes at each centre to identify good practice that can be shared, or, where lower than expected recruitment is seen, determine reasons for this and implement changes to boost recruitment. As part of this, we will talk to clinical teams, current participants, and where appropriate with any patients who have decided not to participate, to fully understand the recruitment figures. Meetings between all participating centres to enable good practice to be shared will be arranged. The process will be overseen by the IDMEC and TSC prior to consideration by the HTA to confirm that the trial should continue.

Stop/Go Criteria:

GREEN: progress to main trial; following the pilot phase we will review trial processes to assess whether any changes could/need to be implemented to improve the trial.

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AMBER: review trial processes to identify implementable changes. This may include retraining centres in trial pathways and procedures. We would discuss with the trial oversight committees and funder about the need to extend the pilot phase to verify resolution of issues, then once progress is satisfactory, continue to the main trial.

RED: abandon the trial if both the trial oversight committees and funder feel this is the appropriate course of action.

	Red	Amber	Green
% Threshold	<70%	70-99%	100%
Total Randomised Trial Recruitment	<147	147-209	210
Average Recruitment Rate (per centre/month)	<1.4 (for top 4 recruiting centres) <1.05 (for other centres)	1.4-1.99 (average for at least 4 recruiting centres) 1.05-1.49(average across all other centres	2 (average for at least 4 centres) 1.5 (average for all other centres
Total number of centres opened	<19	19-24	25

17 Definition of the End of the Trial

The trial will end once:

- The last patient has completed their one-year assessments;
- The trial database is confirmed as locked.

Consent for longer term follow up beyond the trial will be sought at the point of consent.

18 Patient and Public Involvement (PPI)

This trial has been developed in close collaboration with patients and the public.

Several PPI and stakeholder engagement events enabled us to understand and incorporate views to ensure a widely accessible, acceptable trial, able to answer questions highly important to patients and clinical care providers. Sarah Murray, Chair of the National BHF PPI group, is a lay co-applicant; she will ensure inclusion of multiple lay perspectives, meeting regularly with patients (progress and feedback, patient facing materials, dissemination).

We will involve patients at each stage of the trial, including:

Trial Governance: Sarah Murray, Chair of the National PPI Group for the British Heart Foundation (BHF) Clinical Research Collaborative is a lay co-applicant. She will ensure inclusion of multiple lay perspectives, meeting regularly with patients to discuss progress and feedback, patient facing materials and dissemination. Sarah will attend and contribute to Trial Management Group and (as non-independent member) the Trial Steering Committee (TSC)

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meetings. Two independent patients will be invited to join the TSC; they will be supported by Sarah, the CI, and CTU.

Trial participant accessibility, recruitment and retention: patient facing materials have been co-produced with patients to ensure that they are inclusive, and accessible to a wide range of patient groups. We have worked with a range of groups underserved in cardiac surgical research (particularly women). We have consulted with patients on the protocol to try and remove barriers to entry into the trial and enable compliance with the trial procedures. At the end of the pilot, we will speak to participants about their experiences of taking part to understand if changes would improve it for the main trial phase.

Communication: We will maintain clear communication with patients, including using a trial website to ensure that updates, recruitment numbers and milestones are easily accessible to participants.

Dissemination: At the end of the trial, Sarah will bring together patients from her national roles to plan and design the dissemination of findings and collate the patient perspectives on the interpretation of findings. Dissemination of the trial findings to patients will be through a variety of means including through charities such as Heart Valve Voice, Heart Research UK, and the BHF, who all fully support the trial.

19 Equality, Diversity, and Inclusivity

Inclusivity: Recruitment from 25 units in the UK with broad inclusive eligibility criteria will help to enable inclusivity. We will translate information sheets, enable interpreters, and provide travel expenses.

Diversity: The inclusion of women and minority groups in cardiac surgical clinical trials is critical for scientific, ethical, and social reasons and for the generalisability of AFFECT trial results and the trial team are strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity. These groups in particular have been identified as under-served by cardiac surgery research. AFFECT will:

- Monitoring of the number of women and minorities screened and enrolled via screening logs from each clinical centre will be undertaken on a monthly basis.
- Explore any barriers to participation through ongoing discussion and engagement with patient groups and implement solutions throughout the duration of the trial.
- Develop and implement outreach programs designed to recruit adequate numbers of women or minorities, where targets of at least 25% of patients being female and at least 5% of patients being from minority backgrounds are not being met.

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- Provide patients with choices in terms of follow up assessment methods to avoid digital exclusion, or barriers such as transport or distance to attending follow up visits.

20 Remuneration

No direct remuneration will be provided for patients to participate in the trial; however, reimbursement for travel and associated expenses will be available to support participants. The expectation is that most visits at 3 and 12 months, and annually will be via telephone and the protocol makes no requirement for patients to attend the hospital, but a travel budget will be available (of up to £40 per follow up visit for the planned time-points) to support those who wish to attend hospital. Funding is available for up to 10% of patients for two visits each.

21 Monitoring and Quality

Study conduct will be assured with a robust monitoring plan. The study will employ a risk-based monitoring approach, focussing on critical processes to ensure study integrity, participant safety and security, and on data validity.

The Trial Management Group will assess the risk level of the trial and review this at regular intervals throughout the course of the project. This risk assessment will form the basis of the monitoring plan.

Monitoring will be conducted in accordance with the monitoring plan, by ACU representatives trained and competent to do so.

Breaches of study compliance will be reported to the TSC, the Sponsor, and the Research Ethics Committee and MHRA, as necessary. Protocol deviations and violations and any associated recovery and action plans will be documented in study records, namely in Case Report Forms (CRFs), the Investigator Site Files (ISFs) or the Trial Master File {TMF).

22 Information Governance

Participants' personal data shall be treated in confidence and in compliance with the UK Policy Framework for Health and Social Care, the Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR). When processing or archiving personal data, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

Study data will be entered into a web-based electronic data capture (EDC) system (called CASTOR). This application is designed to be in full compliance with the applicable regulations.

Each participant will be assigned a unique identification number upon consent. The trial database and randomisation system will be password protected and only researchers collecting and analysing data will have access to this database. Access to clinical study information will be based on individuals' roles and responsibilities. The HES and ONS data (or

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equivalents) will be stored securely and only researchers processing and analysing data will have access to this.

All personal information will be kept confidential at the recruiting sites unless there is specific consent and approval for transfer of this to another site for study-related purposes.

The dataset for the trial will include:

Date of Birth, Sex at Birth, Medical History, Ethnicity, Postcode, NHS numbers.

For the purposes of completing questionnaires online, the database will also contain participants' personal email addresses through which links to the questionnaires will be sent.

For the purposes of obtaining HES and ONS data, NHS numbers will be needed. Equivalents in the devolved nations may apply.

Screening logs as described in 12.5 will be sent to the ACU through secure NHS email addresses.

Participants may also be sent scanned/completed copies of their consent form via their email address if this is their preference, and their email address may also be used during the remote consent process, if applicable.

Any paper documentation will be stored securely in the relevant research offices at sites. Neither hard copies nor electronic files containing personal information will be removed from the research offices or stored in a non-secure manner electronically.

23 Data Sharing and Data Access

All source data, study documents, participant notes should be made available for monitoring and audits by the Trials Unit, the Sponsor, and local NHS host organisations, and in the event of an inspection by the competent authority.

Study documentation must be retained in a secure location during the conduct of the study.

Personal identifiable data, beyond the minimal data set contained in the database, will be retained for up to 5 years following the end of AFFECT, after which it will be destroyed.

Participants will have the option to consentto longer term follow up beyond the end of the trial. Where participants consent to this, personal data beyond the minimal dataset contained in the database, will be kept until the 5 years after the last data collection for the longer term follow up before being destroyed.

All electronic data will be stored on secure network systems, to which only the relevant site and central study research team staff have access.

For the purposes of this study, South Tees Hospitals NHS Foundation Trust will act as a Data Controller. For any data stored (e.g., HES data) in a Secure Data Environment (SOE), the

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SOE may function as a joint Data Controller with South Tees Hospitals NHS Foundation Trust. Further information will be provided in a study-specific Privacy Notice available on the study website.

At the end of the trial, the trial dataset will be available to other researchers on request and following approval by the Chief Investigator, and Sponsor.

24 Dissemination

The results of the trial are expected to fill an important and large gap in UK NICE guidance and international guidelines and literature, for a condition that affects approximately 50% of the 3000 patients who undergo MVr within the NHS each year.

Stakeholders for the AFFECT research findings include patients, NHS England and the clinical community nationally and internationally. Findings will be disseminated widely to these audiences to maximise opportunities to inform and influence national and international practice. Findings will be reported to the funder, Society for Cardiothoracic Surgery, the guideline writing committees of the American Heart Association and European Society of Cardiology, National Institute for Health and Care Excellence (NICE) and presented at international and national conferences and scientific meetings. We will aim to publish in high impact, open access, and widely read journals.

The Chief Investigator will be responsible for ensuring the results of AFFECT are disseminated through peer reviewed journals once the analyses are complete.

Authorship on the primary findings manuscript and subsequent manuscripts will be in accordance with the guidelines of medical journals and will be confirmed by the TMG, with final approval by the Chief Investigator.

Dissemination of findings to patients will be critical. Sarah Murray (PPI lead) and Prof Wilkes (co-applicant) will optimise dissemination to lay audiences and engagement with primary care respectively. Following the trial, participants will be informed of the results most likely in a letter sent to them directly, which will be approved by TSC patient representatives, and by National Heart Surgery PPI (NCS PPI) group. We will run patient focused webinars to ensure the findings are widely and appropriately disseminated and we will also explore other ways of reaching patients (for example using social media) as the trial develops and tailor our dissemination of trial findings to them accordingly.

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Appendix: Alternative Representation of AE Reporting Requirements

AE	AR	SAE	SAR	SUSAR	Outcome/AE of Special Interest	Reporting Requirements
✓	✓	✓	✓	✓	✓	Expedited reporting
✓	✓	✓	✓	✓	✗	Expedited reporting
✓	✓	✓	✓	✗	✓	Record in EDC
✓	✓	✓	✓	✗	✗	Record in EDC
✓	✓	✗	✗	✗	✓	Record in EDC
✓	✓	✗	✗	✗	✗	Record if Grade 3 or above in EDC
✓	✗	✗	✗	✗	✓	Record in EDC
✓	✗	✗	✗	✗	✗	Do NOT record in EDC
✓	✗	✓	✗	✗	✓	Record in EDC
✓	✗	✓	✗	✗	✗	Record if Grade 3 or above in EDC

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