

Study Protocol

EVoLVeD

Early Valve Replacement guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis

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DOCUMENT HISTORY

Version Number	Version Date	Summary of changes
8.0	19MAR2024	The wording of long-term follow-up endpoints updated to be in keeping with endpoints collected at first database lock. Clarity regarding second database lock added. Clarity added regarding AE/AR reporting and quarterly safety reporting to Sponsor.
7.0	13OCT2023	Extending follow up by remote medical record review up to 20 years for post-hoc analysis. Follow up will include the collection of the primary endpoint and relevant secondary endpoints, repeat aortic valve intervention, unplanned hospitalisation due to structural valve degeneration and evidence of structural valve degeneration.
6.0	06APR2023	Clarification of extended follow up beyond database closure of the main study, for the purposes of post-hoc analysis. Minor corrections. Change of trial manager.
5.0	28JAN2020	Addition of co-enrolment to EASY-AS. Extension of recruitment period. Clarification to sample size calculation and proposed analysis because of extension and co-enrolment to EASY-AS. Minor corrections.
4.0	01MAY2018	Update of contact details. Addition of screening method as a minimisation variable. Addition of document history section. Addition of PI signature section. Update to ECG LVH criteria. Update to allocation ratio in groups C&D. Minor corrections.
3.0	21AUG2017	Updated screening criteria in ECG only sites from LVH+strain to LVH only. Change in ECG LVH criteria from Romhilt-Estes to Peguero-Lo Presti. Changing the cut off for high sensitivity troponin from >6.0 to ≥6ng/L. Reducing the stated desired maximum interval between randomisation to early intervention and performing the intervention from 4 to 2 months. Inclusion of a participant invitation letter.
2.0	11MAY2017	Clarification of time required to consider consent (section 5.2). Minor corrections.
1.0	21MAR2017	N/A – new document

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PROTOCOL APPROVAL

EVoLVeD: Early Valve Replacement guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis

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LIST OF ABBREVIATIONS

ACCORD	The Academic and Clinical Central Office for Research & Development
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CHI	Community Health Index
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
EASY-AS	A Randomised Controlled Trial of Early valve replacement in severe ASYmptomatic Aortic Stenosis
ECG	Electrocardiography
ECTU	Edinburgh Clinical Trials Unit
EFS	Edmonton Frail Scale
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
hsTnI	High Sensitivity Troponin I
HF	Heart Failure
ISF	Investigator Site File
LGE	Late Gadolinium Enhancement
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
PMG	Project Management Group
PROBE	Parallel-group multicentre prospective randomised open-label blinded endpoint
RBH	Royal Brompton Hospital

REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIGN	Scottish Intercollegiate Guidelines Network
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAVI	Transcatheter Aortic Valve Implantation
TMF	Trial Master File
TSC	Trial Steering Committee
WHODAS	World Health Organisation Disability Assessment Schedule

SUMMARY

Professional Summary

Design: A parallel-group multicentre prospective randomised open-label blinded endpoint (PROBE) controlled trial of early aortic valve intervention in asymptomatic patients with severe aortic stenosis (AS) and evidence of left ventricular (LV) decompensation (mid-wall fibrosis) on cardiac magnetic resonance imaging (MRI), with an observation arm of patients without evidence of LV decompensation on cardiac MRI.

Setting: Hospitals in Scotland and England.

Target Population:

Inclusion criteria: 1. Severe aortic stenosis (aortic valve peak velocity ≥4.0 m/s, or aortic valve area indexed to body surface area <0.6cm^2/m^2 with aortic valve peak velocity ≥3.5m/s) 2. Age over 18 years 3. No symptoms attributable to aortic stenosis that require aortic valve replacement

Exclusion criteria: 1. Deemed lower risk for mid-wall fibrosis on screening 2. Planned cardiac surgery 3. Previous valve replacement 4. Severe hypertension (systolic >180 or diastolic >110 mmHg) 5. Acute pulmonary oedema or cardiogenic shock 6. Left ventricular ejection fraction <50% on cardiac MRI 7. Significant abnormalities on cardiac MRI that would prevent enrolment 8. Coexistent severe aortic regurgitation or mitral regurgitation 9. Coexistent mitral stenosis greater than mild in severity 10. Coexistent hypertrophic cardiomyopathy or cardiac amyloidosis 11. Any contraindication to MRI scanning 12. Advanced renal impairment 13. Pregnancy or breast feeding 14. Patient judged to be unfit to be considered for aortic valve replacement or transcatheter aortic valve implantation 15. Patient declines to consider undergoing valve replacement surgery or transcatheter aortic valve implantation 16. Inability to give informed consent 17. Previous randomisation into this study

Health technologies being assessed: Use of aortic valve intervention (surgical aortic valve replacement or transcatheter aortic valve implantation) in patients with asymptomatic severe aortic stenosis with evidence of LV decompensation.

Measurement of outcome

Primary outcome: Composite of all-cause mortality or unplanned aortic stenosis-related hospitalisation between randomisation and final follow up visit for study participants with mid-wall fibrosis.

Secondary outcomes: 1. Mortality: all-cause, cardiovascular, AS-related, and sudden cardiac death. 2. Unplanned aortic-stenosis related hospitalisation. 3. Symptomatic status as assessed by NYHA functional classification. 4. Health and disability status as assessed by the WHODAS 2.0. 5. The development of systolic LV dysfunction. 6. Stroke 7. Permanent pacemaker insertion, cardiac resynchronisation therapy or automated implantable cardioverter defibrillator. 8. Endocarditis 9. 30 day post-operative complications following aortic valve intervention

Sample size: Using a logrank approach with a hazard ratio of 2, we will need to observe 88 primary outcome events to give us 90% power at 5% significance level. We aim to recruit up to 400 participants with midwall fibrosis and follow them up for up to 7 years.

Lay Summary

The aortic valve can be thought of as a one-way door through which blood leaves the heart to enter the body. It has to be able to open well to allow blood out and close properly to stop blood leaking back and overloading the heart.

Aortic stenosis is a condition where the aortic valve becomes progressively narrowed (stenosed; i.e. the door doesn't open very well) usually over a number of years or decades. This is usually caused by hardening and thickening of the valve so that it becomes less flexible. This puts a strain on the heart muscle as it has to work harder to "open the door" and pump blood through the narrowed valve. For many years the heart adapts and copes with this increased pressure but eventually it is no longer able to cope and patients develop symptoms (chest pain, breathlessness, collapse) and an increased risk of heart failure and dying. The only treatment currently available for severe aortic stenosis is surgery to replace the narrowed valve. The timing is key: replace the valve too early and patients are put through surgery and the risk of a replacement valve without reason; too late and patients may be left with irreversible symptoms and heart failure. At the moment we replace the valve when patients first develop symptoms but these can be tricky to assess in patients with lots of other health conditions or in those that are inactive. As a consequence the timing of aortic valve operations is often suboptimal.

Fibrosis or scarring of the heart is one of the key processes that causes the heart to fail in this condition. Scarring once formed does not appear reversible, so any scar that forms prior to valve replacement will remain with the patient even after surgery. Using cardiac MRI (a completely safe method of scanning the heart involving strong magnetic fields and lying in a tunnel) we are able to detect the earliest stages of this scarring. We believe this will identify patients whose hearts are starting to fail (even before they develop symptoms) and who therefore need prompt replacement of their valves.

In our study we will use cardiac MRI to look for heart scarring in patients with severe aortic stenosis but no symptoms. Patients with confirmed heart scarring will then be randomised to either early valve replacement surgery or to the current treatment strategy. This consists of continued monitoring of the valve over time waiting for patients to develop symptoms.

We believe that performing aortic valve replacement on patients with severe aortic stenosis with no symptoms but who have evidence of early scarring on cardiac MRI will prevent further scarring from forming, reduce subsequent heart failure and lead to improved long-term symptoms following surgery (e.g. breathlessness) and a reduced chance of dying. The aim of this trial is to find out whether this is correct.

1 INTRODUCTION

1.1 BACKGROUND

Aortic stenosis is the most common form of valve disease in the western world. It is already a major health care burden [1,2] but, with an ageing population, is set to treble by the year 2050. In the initial phases, the increased afterload imposed by aortic valve narrowing induces adaptive LV hypertrophy that acts to maintain wall stress and cardiac output. Ultimately, this process decompensates and patients transition from hypertrophy to heart failure and the development of symptoms and adverse cardiovascular events [3-5].

Yet despite the prevalence of aortic stenosis, we lack effective medical therapies. Indeed, the only treatment option available is replacement of the valve using either surgical or percutaneous techniques. Judicious timing of aortic valve replacement (AVR) is crucial. Too early and patients are exposed unnecessarily to the significant morbidity and mortality associated with prosthetic heart valve replacement surgery. Too late and patients will sustain irreversible damage to their heart muscle that translates in to an increase in post-operative complications, the development of heart failure and an adverse long-term prognosis. Current guidelines recommend AVR in patients with severe stenosis and evidence of left ventricular decompensation. Traditionally the latter is defined by the development of symptoms and/or a fall in ejection fraction. However, both of these criteria are outdated and have major limitations. Symptoms are subjective and frequently difficult to interpret in elderly patients, whilst a reduction in ejection fraction is often a late and irreversible phenomenon [6].

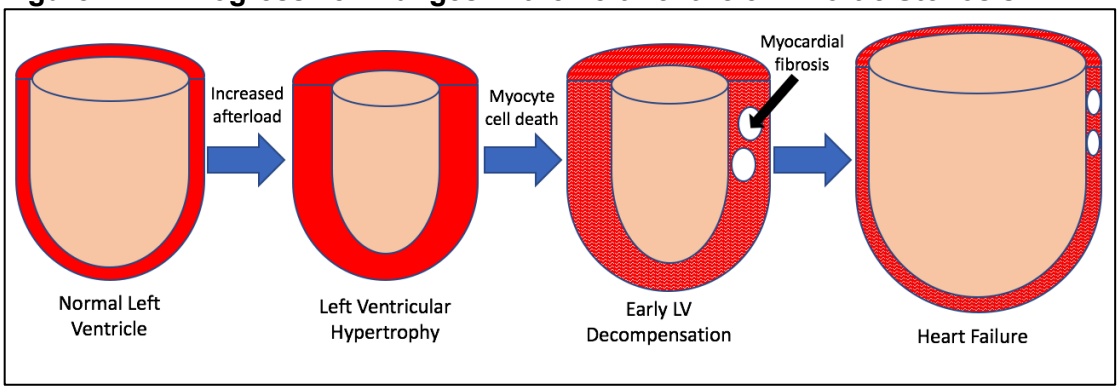
There is therefore a major unmet clinical need for more objective and specific markers of LV decompensation that can more accurately define the optimum timing of AVR. The purpose of this study is to address these key issues and ultimately to improve the care of patients with aortic stenosis.

1.2 RATIONALE FOR STUDY

The development of symptoms and adverse events in aortic stenosis relates to how the left ventricle adapts to the associated increases in afterload. Indeed aortic stenosis triggers a hypertrophic response in the myocardium that initially restores wall stress and maintains cardiac performance, but eventually leads to decompensation, driving the transition to heart failure, symptoms and ultimately death (Figure 1—1). Importantly only a weak association exists between the magnitude of the hypertrophic response and the severity of valve obstruction, making it important that both processes are considered independently.

In conditions associated with left ventricular pressure overload such as aortic stenosis and hypertension, myocyte size and myocardial wall thickness increase to restore wall stress. This hypertrophic response is initially adaptive maintaining cardiac output and systolic function. However as hypertrophy increases, the left ventricle ultimately decompensates, leading to progressive impairment in ventricular performance and the development of symptoms and adverse cardiovascular events. Histological studies have indicated that this pathologic transition from ventricular adaptation to decompensation is driven primarily by two processes: myocyte death and myocardial fibrosis. Myocyte death takes the form of apoptosis and necrosis (cell swelling and loss of membrane integrity sometimes referred to as oncosis in this context), and is accompanied by signs of cellular stress manifest as increased autophagy.

Figure 1—1: Progressive Changes in the Left Ventricle in Aortic Stenosis



Replacement myocardial fibrosis is believed to occur in response to cell death and the ensuing inflammation. Such fibrosis is irreversible and its accumulation in the ventricle leads to progressive impairment of myocardial relaxation (diastolic dysfunction) and contraction (systolic dysfunction), driving the clinical progression to heart failure.

The presence of myocardial fibrosis can be assessed non-invasively using cardiac MRI and the late gadolinium enhancement (LGE) technique. Following an intravenous bolus, gadolinium partitions and accumulates within the extra-cellular volume. This is particularly prominent where the extracellular volume has expanded, such as areas of replacement myocardial fibrosis, and is detectable on T1-weighted cardiac MRI. Studies examining myocardial biopsy samples have shown a good correlation between histological myocardial fibrosis and LGE on cardiac MRI [7]. Importantly, the presence of LGE in patients with severe aortic stenosis is an independent predictor of all-cause mortality [7-9].

Although cardiac MRI is non-invasive and safe, it is time consuming, expensive and access is still limited in many centres across the United Kingdom. We have recently demonstrated that two routinely used markers, plasma high sensitivity cardiac troponin I (hsTnI) concentration and the ECG (presence of voltage criteria for left ventricular hypertrophy [ECG-LVH] and the ECG-strain pattern) are independently associated with mid-wall myocardial fibrosis on cardiac MRI and adverse cardiovascular events [10,11].

We therefore propose that in a population with severe asymptomatic aortic stenosis, (who currently do not meet guideline indications for surgery) that screening with the ECG and hsTnI will identify patients with an increased probability of mid-wall myocardial fibrosis and LV decompensation as identified on subsequent cardiac MRI. With current management strategies, these patients are at increased risk of adverse cardiovascular events and all-cause mortality. We hypothesise that early aortic valve intervention in this group will limit progression of myocardial fibrosis, halt the transition to heart failure and lead to improved patient outcomes compared to routine clinical management.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

- To determine whether early aortic valve replacement can reduce death and unplanned AS-related hospital admissions in patients with asymptomatic severe aortic stenosis who have subclinical but objective evidence of LV decompensation.

2.1.2 Secondary Objectives

- To determine whether early aortic valve replacement in patients with asymptomatic severe aortic stenosis who have subclinical but objective evidence of LV decompensation improves other clinical outcomes (see section 2.2.2) including death and unplanned AS considered separately, long-term symptomatic status, post-operative outcomes and reduces the development of LV dysfunction.
- To determine whether amongst patients receiving routine care, those with mid-wall fibrosis develop symptoms more quickly or have worse clinical outcomes compared to those without fibrosis.

2.1.3 Exploratory Objectives

- To explore the association between clinical factors, cardiac biomarkers and cardiac MRI characteristics in patients with aortic stenosis.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- Composite of all-cause mortality or unplanned aortic stenosis-related hospitalisation between randomisation and final follow up visit for study participants with mid-wall fibrosis.

Unplanned aortic stenosis-related hospitalisation is defined as an unplanned admission with syncope, heart failure, chest pain or arrhythmia (ventricular arrhythmia or second or third degree heart block) attributed to aortic stenosis. This endpoint will be independently adjudicated by two investigators blinded to the details of randomisation (see section 10.5).

2.2.2 Secondary Endpoints

- Mortality: all-cause, cardiovascular, AS related, and sudden cardiac death between randomisation and final follow up visit
- Unplanned aortic-stenosis related hospitalisation between randomisation and final follow up visit
- Health and disability as assessed by the 12-item WHO Disability Assessment Schedule 2.0 (WHODAS) at the 1 year visit.
- The development of LV systolic dysfunction (ejection fraction <45% quantitatively or at least moderate LV dysfunction qualitatively) between randomisation and final follow up visit.
- Symptomatic status as assessed by NYHA functional classification at the 1 year visit.

- Permanent pacemaker insertion, cardiac resynchronisation therapy or automated implantable cardioverter defibrillator between randomisation and final follow up visit
- Stroke between randomisation and final follow up visit
- Endocarditis between randomisation and final follow up visit
- 30 day post-operative complications following aortic valve intervention (safety end-point, appendix A).

Cardiovascular mortality is defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, or other cardiovascular causes, death related to cardiovascular procedures, and death due to other cardiovascular causes.

AS-related death is a death where aortic stenosis has been listed as a contributory cause by the clinical care team on the patient's official death certificate.

Sudden cardiac death is defined as any death that occurs unexpectedly and not within 30 days of acute myocardial infarction (MI). This includes unsuccessful resuscitation following an arrhythmia. (see appendix B for full list [12]).

Stroke is defined as any new rapid-onset focal or global neurological deficit (change in conscious level, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia, visual loss, or any other sign consistent with a stroke) persisting greater than 24 hours or with brain imaging compatible with new infarction or haemorrhage.

Endocarditis is defined as a clinical diagnosis of endocarditis by the treating physician and have at least one positive blood culture for a typical endocarditis organism (e.g. staphylococcus or streptococcus species).

Secondary endpoints will be analysed in groups A, B and C.

2.2.3 Exploratory Endpoints

Blood samples will be obtained and stored from consented participants to gain a greater understanding of the pathophysiology of aortic stenosis. These will be used to analyse biochemical markers associated with cardiac disease (e.g. Brain Natriuretic Peptide (BNP), hsTnI). Cardiac MRI parameters (such as LV mass, ejection fraction and T1 mapping measures) and their relationship with clinical factors and other biomarkers will also be analysed. In addition, genetic analysis will be performed to assess for gene associations with myocardial fibrosis / LV decompensation.

2.2.4 Long-term remote follow up for post-hoc analysis

Follow up via remote medical record review will be conducted annually for approximately 10 years, to identify potential valve degeneration and associated morbidity and mortality as post-hoc analysis.

Primary endpoint for post-hoc analysis

- Composite of all-cause mortality or unplanned aortic stenosis-related hospitalisation between randomisation and follow up for study participants with mid-wall fibrosis.

Secondary endpoint for post-hoc analysis

- Mortality: all-cause, cardiovascular, AS related, and sudden cardiac death between randomisation and follow up.
- Unplanned aortic-stenosis related hospitalisation between randomisation and final follow up visit.
- The development of LV systolic dysfunction (ejection fraction <45% quantitatively or at least moderate LV dysfunction qualitatively) between randomisation and follow up.

- Permanent pacemaker insertion, cardiac resynchronisation therapy or automated implantable cardioverter defibrillator between randomisation and final follow up visit.
- 30 day post-operative complications following aortic valve intervention (safety end-point, appendix A).
- Stroke.
- Endocarditis.
- Repeat aortic valve intervention (re-do surgical aortic valve replacement or transcatheter aortic valve replacement).
- Evidence of structural valve degeneration.

3 STUDY DESIGN

This will be a parallel-group multi-centre prospective randomised open label blinded endpoint (PROBE) controlled trial with an additional observational arm. Randomisation will be 1: 1 among those with mid-wall fibrosis being randomised into the two arms of the full study, and will use a flexible, adaptive randomisation ratio among those without mid-wall fibrosis being randomised into the observational arm or no further follow up.

Patients with severe aortic stenosis attending outpatient clinics or echocardiogram appointments will be identified and assessed for eligibility. Participants may also be identified by participating centres from local databases – these participants can be invited to take part by sending a letter from their normal care team. Potential participants meeting the inclusion criteria and demonstrating normal left ventricular ejection fraction (LVEF) on routine echocardiography can be approached about participating in study.

Potential participants will undergo an initial screening assessment based upon troponin I measurements and/or the ECG. This will determine whether potential participants are considered *lower-risk* or *higher-risk* for the presence of mid-wall myocardial fibrosis on cardiac MRI. At sites where the Abbott high sensitivity troponin I assay is available patients will be considered at higher risk if they demonstrate ECG-LVH with strain and/or elevated troponin levels (≥6ng/L). At sites where the Abbott high sensitivity troponin I assay is not available then patients at that site will be screened using the ECG only (ECG only sites). At these sites the presence of voltage criteria for LVH on the ECG (ECG-LVH) **with or without strain** will be used to define patients at higher risk.

Patients at *lower-risk* (without ECG-LVH with strain and troponin levels <6ng/L at sites with access to hsTnI; or patients without ECG-LVH at the ECG only sites) will be considered to have a healthy myocardium and no suggestion of LV decompensation. These patients will take no further part in the study but their details will be retained by the research team for future record linkage.

Patients at *higher-risk* will undergo baseline assessments including cardiac MRI.

If a participant is still eligible following baseline assessment and no other exclusion criteria are identified on central cardiac MRI review (see section 5.5.5), then the participant can be enrolled into the study. If the central cardiac MRI review demonstrated mid-wall myocardial fibrosis then the participant will be randomised 1:1 to early treatment or routine care. These patients will be followed up in the study annually.

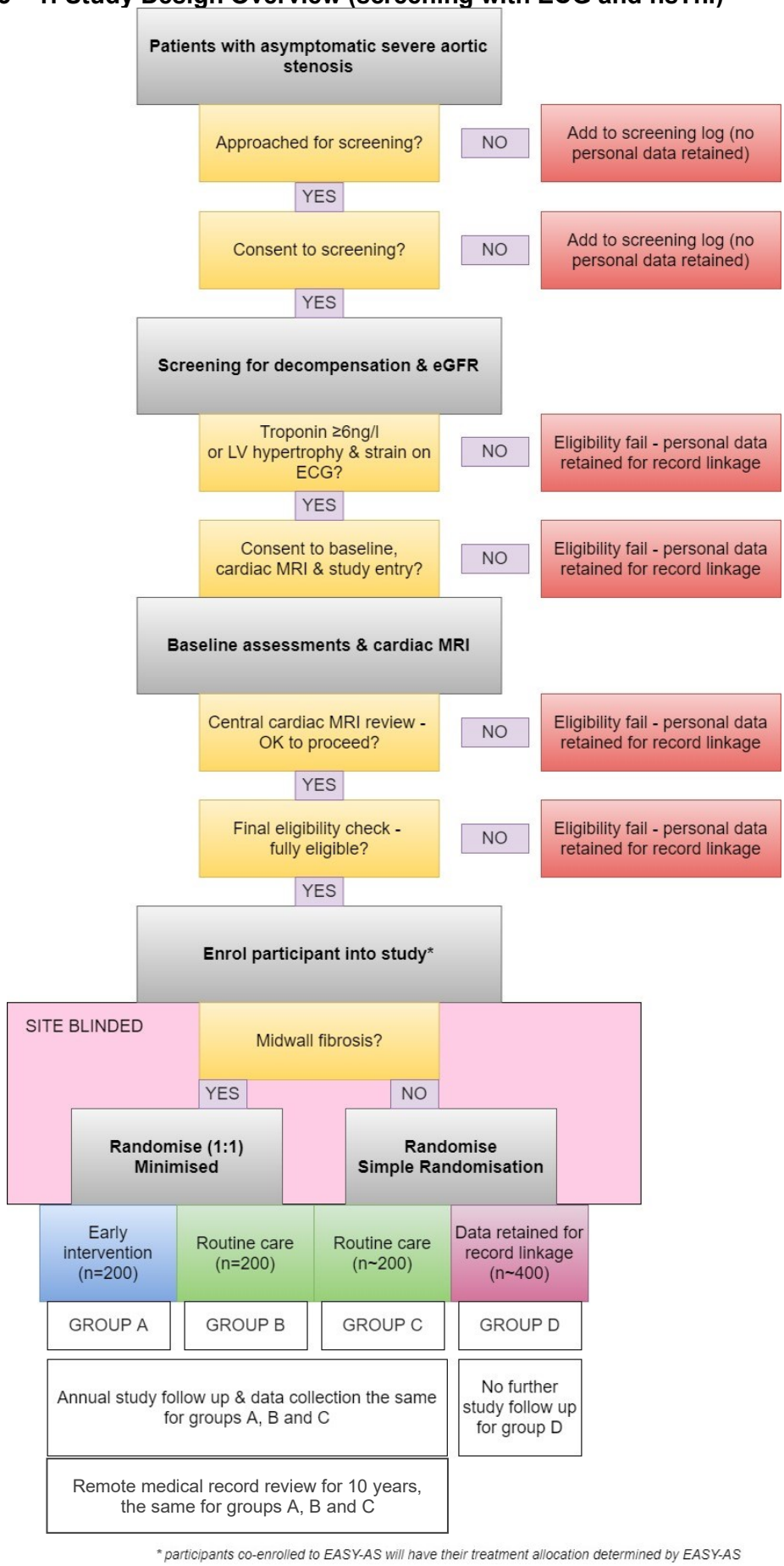
If no mid-wall fibrosis is detected on central cardiac MRI review then participants will be entered into an observational arm using a flexible, adaptive randomisation ratio, aimed at balancing those in the observational arm and the routine care arm. Those who do not enter the observational arm will have no further study follow up but their data will be retained for future data linkage. Those entered into the observational arm will have the same study follow up schedule to those participants with mid-wall fibrosis.

As well as providing key mechanistic insight, this approach will also maintain the patient and physician blinding as to the presence or absence of mid-wall fibrosis on cardiac MRI in patients undergoing follow up who are not randomised to early valve intervention.

Participants who have been assessed as eligible for both EVoLVeD and EASY-AS (A Randomised Controlled Trial of Early valve replacement in severe ASYmptomatic Aortic Stenosis) and have consented to both studies will be enrolled into EVoLVeD based on their randmisation allocation in EASY-AS, either AVR (early intervention) or Expectant Management (routine care). All participants in this group will have study follow up.

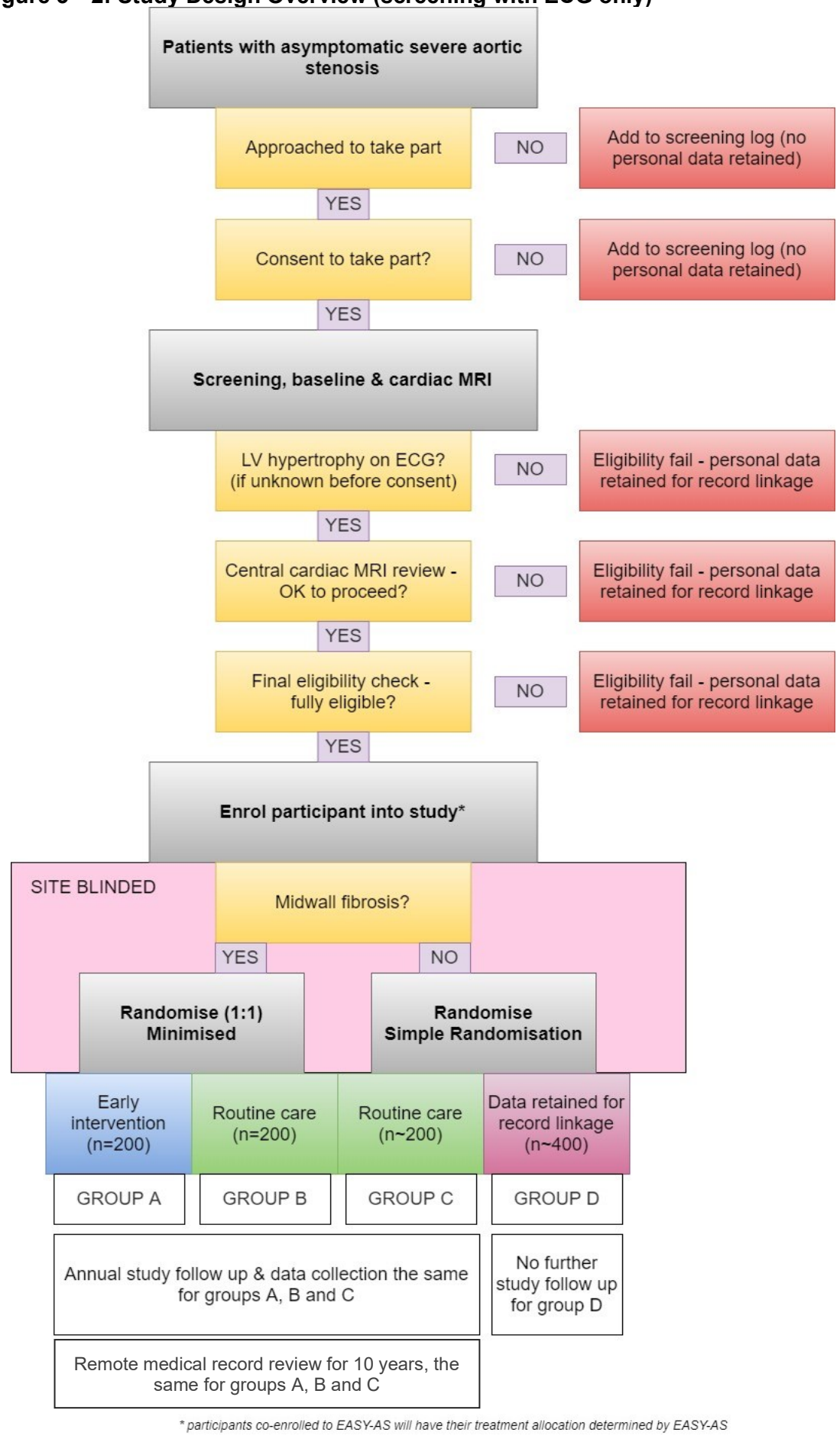
Long-term follow up of participants for the purposes of post-hoc analysis will occur annually via a remote medical record review, for participants in groups A, B and C. Participants will not be contacted for this.

Figure 3—1: Study Design Overview (screening with ECG and hsTnI)



** participants co-enrolled to EASY-AS will have their treatment allocation determined by EASY-AS*

Figure 3—2: Study Design Overview (screening with ECG only)



** participants co-enrolled to EASY-AS will have their treatment allocation determined by EASY-AS*

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The sites taking part in this study are listed in the Participating Sites document.

We aim to screen patients with asymptomatic severe aortic stenosis (aortic valve peak velocity ≥4.0 m/s on Doppler echocardiography or aortic valve area indexed to body surface area <0.6cm^2/m^2 with aortic valve peak velocity ≥3.5 m/s) and preserved LV systolic function to identify patients with evidence of LV decompensation to proceed to cardiac MRI. Those meeting the eligibility criteria will be enrolled into the study. 400 participants with mid-wall fibrosis will be randomized 1:1 to receive early valve intervention or routine care. Amongst those without mid-wall fibrosis (approximately 600), 200 participants will enter an observation arm and up to 400 will not be followed up but their data will be retained for future data linkage. The planned recruitment period is 5 years.

4.2 INCLUSION CRITERIA

For inclusion in the study, participants should fulfil the following criteria:

1. Severe aortic stenosis (aortic valve peak velocity ≥4.0 m/s, or aortic valve area indexed to body surface area <0.6cm^2/m^2 with aortic valve peak velocity ≥3.5m/s)
2. Age over 18 years
3. No symptoms attributable to aortic stenosis that require aortic valve replacement

4.3 EXCLUSION CRITERIA

Participants cannot be enrolled into the study if any of the following criteria are fulfilled:

1. Deemed lower risk for mid-wall fibrosis on screening
2. Planned cardiac surgery
3. Previous valve replacement
4. Severe hypertension (systolic >180 or diastolic >110 mmHg)
5. Acute pulmonary oedema or cardiogenic shock
6. Left ventricular ejection fraction <50% on cardiac MRI
7. Significant abnormalities on cardiac MRI that would prevent enrolment (see section 5.5.5)
8. Coexistent severe aortic regurgitation or mitral regurgitation
9. Coexistent mitral stenosis greater than mild in severity
10. Coexistent hypertrophic cardiomyopathy or cardiac amyloidosis
11. Any contraindication to MRI scanning (such as permanent pacemaker)
12. Advanced renal impairment (glomerular filtration rate <30 mL/min/1.73 m^2)

13. Pregnancy or breast feeding
14. Patient judged to be unfit to be considered for aortic valve replacement or transcatheter aortic valve implantation
15. Patient declines to consider undergoing valve replacement surgery or transcatheter aortic valve implantation
16. Inability to give informed consent
17. Previous randomisation into this study

4.4 CO-ENROLMENT

Co-enrolment will be considered on a case-by-case basis and will consider the extra burden being placed on the study participants and the likelihood of study assessments or interventions influencing the outcomes of either study. The Sponsor's representatives require Investigators from all studies involved in co-enrolment to be aware of the co-enrolment plans and provide documented permission for co-enrolment to be undertaken in their study.

The acceptability of co-enrolment with some specific trials are now considered:

- SALTIRE 2 (a randomised controlled trial of bisphosphonates/denosumab versus placebo on the progression of mild to moderate aortic stenosis) – co-enrolment will not be permitted as both studies could directly affect outcome measures of the other. No wash out time is required following the end of a participant's involvement in SALTIRE 2.
- MODE-AS (observational study of patients undergoing AVR with intraoperative myocardial biopsy) – co-enrolment is permitted as there is significant overlap in study assessments leading to minimal extra burden on patients.
- COMPASS (observational study of patients with asymptomatic moderate to severe aortic stenosis) – co-enrolment will be permitted on a case-by-case basis following discussion between investigators.
- EASY-AS – co-enrolment is permitted between EVoLVeD and EASY-AS when participants are being recruited to both trials at the same time. In this situation the randomisation allocation from EASY-AS will be accepted. However participants will not be randomised into EASY-AS until the CMR imaging within the EVoLVeD trial is complete.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified and recruited from the cardiology outpatient clinics or echocardiogram lists at participating centres with the aid of local databases (participants can be invited by sending a letter from their normal care team). When identifying potential participants for screening an echocardiogram demonstrating severe aortic stenosis performed within the previous three years is acceptable. However, if a patient proceeds to baseline assessment and no echocardiogram result is available dated within the previous 6 months, an echocardiogram should be performed at the baseline visit.

5.2 CONSENTING PARTICIPANTS

Potential participants will be approached for consent by the site Principal Investigator or appropriate qualified individual to whom this task has been delegated. This will include research nurses and practitioners if compatible with local policy. Once participants have had adequate time to consider the information and ask questions written consent will be sought. Potential participants can be consented on the same day for screening, but should be given at least 24 hours to consider entering the main trial.

The consent process will vary depending on access to the Abbott high sensitivity troponin I assay. When screening with both the ECG and the Abbott high sensitivity troponin I assay there will be two-step consenting process:

- **Consent to screening for risk of mid-wall fibrosis**
  Potential participants who meet the inclusion criteria and have preserved LV systolic function will be supplied with the Screening Participant Information Sheet (Part A) and Consent Form. If consent is given, this will allow for demographic data to be collected and screening procedures including venepuncture to take place to determine risk of mid-wall fibrosis (see section 5.3).

- **Consent to Baseline, Cardiac MRI and trial entry**
  Those patients deemed to be at *higher-risk* for mid-wall myocardial fibrosis following screening will be invited to attend for baseline assessment. Written informed consent will be obtained before any study related procedures are performed. Details of the baseline assessments can be found in section 6.2.

This 2-step consent process will allow us to screen patients with troponin quickly and efficiently in the clinic. In those found to be eligible, a more detailed second stage consent process will then ensue before participation in the main part of the clinical trial.

When screening without the Abbott high sensitivity troponin I assay (i.e. ECG only), consent will be simplified to a single step and any study-specific activities will be carried out after this consent.

5.3 SCREENING FOR MID-WALL FIBROSIS RISK

The following investigations will be carried out for screening:

1. A standard **12-lead electrocardiogram (ECG)**,

    - If the participant's most recent ECG is within 6 months of screening and is interpretable then there is no requirement to repeat the ECG at screening.

2. **Blood high sensitivity troponin I (hsTnI) concentration**

    - This is a marker of myocardial injury using the Abbott ARCHITECT*STAT* assay. The level of detection of this assay is 1.2 ng/L and the coefficient of variation is <10% at 4.7 ng/L.

    - When screening without the Abbott high sensitivity troponin I assay (i.e. at ECG only sites), a serum sample should still be collected for storage

at ≤-70^{0}C to enable retrospective evaluation of baseline hsTnI concentration. This storage sample can be performed at the baseline assessment.

3. A blood sample will be taken according to local policy to determine eGFR. This is to check suitability for cardiac MRI scanning if the participant proceeds to baseline assessment. If the participant's most recent eGFR result is ≥30 mL/min/1.73 m^2 and within 12 months of screening then there is no requirement to repeat eGFR at screening unless the investigator makes a clinical judgment that a more contemporary result is needed.

The screening process will allow us to stratify patients as *lower risk* or *higher risk* of mid-wall myocardial fibrosis which is defined as the presence of mid-wall late gadolinium enhancement on cardiac MRI. Importantly, there are two methods of screening depending on local availability of the Abbott hsTnI assay. Consequently some sites will screen with troponin/ECG whilst others will screen with the ECG only.

In centres screening with both hsTnI **and** ECG, patients will be deemed at *higher-risk* in the presence of either:

- **A high-sensitivity troponin I concentration** of ≥6 ng/L

- **LV hypertrophy and LV strain pattern on 12-lead electrocardiogram**. LVH will be defined according to standard ECG criteria (including but not limited to the Peguero-Lo Presti criteria [S_D+SV_4 ≥2.8 mV in males, ≥2.3 mV in females][13]; Sokolow-Lyon index; Cornell voltage criteria; and Romhilt-Estes point score system). Patients with left bundle branch block, in whom these criteria cannot be applied, will be assumed to meet ECG criteria for LVH. LV strain will be defined by the presence of LVH with ≥1mm concave downsloping ST segment depression with asymmetrical T wave inversion in at least two contiguous lateral leads.

In centres where local hsTnI testing is not available and **screening is performed using ECG only**, *higher-risk* will be defined as:

- **LV hypertrophy pattern on 12-lead electrocardiogram**, as determined using standard ECG criteria for LVH with or without the strain pattern (see above). Patients with left bundle branch block, in whom these criteria cannot be applied, will be assumed to meet ECG criteria for LVH.

Patients at *higher-risk* for mid-wall myocardial fibrosis and with eGFR ≥30 mL/min/1.73 m^2 will be invited to have baseline assessments and undergo cardiac MRI imaging (see section 6.2).

If the patient does not meet the above higher-risk criteria they will be considered *lower-risk* for mid-wall myocardial fibrosis and will not take further part in the study at this point, but may be re-screened in the future. Their personal information will be retained for potential future data linkage on the outcomes of those who are considered lower-risk for mid-wall myocardial fibrosis.

If for any reason the screening investigations do not provide a result but the participant is still considered at higher-risk for mid-wall myocardial fibrosis then they can proceed to baseline assessments. Missing results should be repeated at the baseline visit, noting that an eGFR result is needed prior to cardiac MRI.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Potential participants meeting the inclusion criteria and demonstrating normal LVEF on routine echocardiography but who do not consent to any part of the study will be recorded on the study screening log. All patients who consent to any part of the study will be entered into the study database. Ineligible and non-recruited patients will continue to be seen by their cardiologist as part of standard clinical care.

5.5 ENROLMENT AND RANDOMISATION

5.5.1 Enrolment and Randomisation Procedures

Following completion of baseline assessments, cardiac MRI and central MRI review, patients that meet all inclusion/exclusion criteria will be enrolled into the study. A web-based computer-generated randomisation process will be employed. There are two separate randomisations, one for patients with mid-wall fibrosis (Randomisation 1) and another for those without mid-wall fibrosis (Randomisation 2).

5.5.2 Randomisation 1 – Patients with Mid-Wall Fibrosis

We will randomise patients in a 1:1 ratio to either early intervention (group A) or routine clinical care (group B). Minimisation techniques will be employed to ensure balancing of key variables: age, sex, aortic valve peak velocity, ischaemic heart disease and screening method (ECG and hsTnI or ECG only).

Group A: Early intervention (200 patients)

Patients will be referred immediately for aortic valve intervention. The choice of either surgical aortic valve replacement or transcatheter aortic valve implantation (TAVI) will be made by the local clinical team according to local policies. In patients undergoing surgical replacement the choice of surgical technique and type of valve replacement used will be at the discretion of the operating surgeon and the patient. Patients found to have significant coronary artery disease requiring concomitant coronary artery bypass surgery will not be excluded. Similarly the choice of TAVI valve and need for percutaneous coronary intervention will be made by the TAVI heart team. The procedure should be performed as soon as possible and ideally within two months of randomisation and allocation to group A. Participants will be followed up in the study as described in section 6.3.

Group B: Routine care (200 patients)

Patients will be invited back for clinical follow up according to local policy. Decision-making regarding future aortic valve intervention will be taken by the participant's clinical team (cardiologist and cardiac surgeon). Participants will be followed up in the study as described in section 6.3.

5.5.3 Randomisation 2 – Patients without Mid-Wall Fibrosis

We will randomise patients using a flexible, adaptive ratio to either routine clinical care (group C) or no further study follow up (group D). The aim of the randomisation ratio is to balance the number of participants in group C and group B. This will be a simple randomisation. Details of the randomisation ratio value, and dates of change will be recorded.

Group C: Routine care (approximately 200 patients)

Patients will be invited back for clinical follow up according to local policy. Decision-making regarding future aortic valve intervention will be taken by the patient's clinical team (cardiologist and cardiac surgeon). Participants will be followed up in the study as described in section 6.3. Group C will appear identical to Group B (see section 5.5.5).

Group D: No further study follow up (approximately 400 patients)

Patients will be invited back for clinical follow up according to local policy. Decision-making regarding future aortic valve intervention will be taken by the patient's clinical team (cardiologist and cardiac surgeon). No further study follow up will take place but personal data will be retained for future data linkage.

5.5.4 Enrolment – Patients already randomised to EASY-AS

Where willing and able, patients will consent to EVoLVeD and EASY-AS at the same time. Patients who have been co-enrolled and randomised to EASY-AS will be enrolled into EVoLVeD based on their allocation in EASY-AS, either early intervention ("aortic valve replacement") or routine care ("expectant management"). All participants in this group will have study follow up.

5.5.5 Blinding of the Routine Care Group and Cardiac MRI Result

The patient and clinical team will be blinded to the central cardiac MRI review and result. This is to ensure that this does not influence future treatment for participants with mid-wall fibrosis who are allocated routine care. If mid-wall fibrosis is present, the patient will undergo Randomisation 1. If randomised to early intervention (Group A), the patient will be aware they have mid-wall fibrosis as they will be referred to a surgeon for consideration of valve replacement.

If mid-wall fibrosis is not present, the patient will undergo Randomisation 2. If randomised to no study follow up (Group D), the patient will be aware they do not have mid-wall fibrosis and will have no further follow up in the study.

However if patients are allocated to routine care groups (B or C) the patient and clinical team will simply be told that they have been allocated routine care and not informed if they are in group B or C. Groups A, B and C will have the same follow up which will maintain patient blinding in groups B and C.

Patients who have been co-enrolled and randomised using the EASY-AS randomisation system will be blinded to the cardiac MRI result regardless of their study allocation.

The clinical care team will also remain blinded to the cardiac MRI result and allocation to routine care groups ensuring that the presence or absence of fibrosis does not influence clinical decision-making. The cardiac MRI scans will be reviewed centrally prior to enrolment. Any clinically significant cardiac findings that would prevent enrolment or influence patient management will be made available to the clinical team.

This includes but is not limited to:

- Impaired LV ejection fraction <50%
- Intracardiac thrombus
- Intracardiac or extracardiac malignancy

- Significant valve disease not appreciated on echocardiography (e.g. severe eccentric aortic regurgitation)
- Significant aortic pathology likely to require surgical repair.

Any local reporting of the cardiac MRI back to the clinical care team should be limited to non-cardiac findings and should specifically not report on the presence or absence of mid-wall fibrosis.

5.5.6 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator, but participants are not required to withdraw solely because they have been non-adherent with the randomised treatment or follow up plan. If withdrawal occurs, the nature and reason for withdrawal will be documented on a change of status form. Any data collected until this point will be retained and analysed unless the participant specifically withdraws consent for this. Participants will be followed up for the primary outcome according to group allocation regardless of their adherence to treatment strategy, unless they withdraw their consent for this.

If a participant, who has given informed consent, loses capacity to consent during the study they should be withdrawn. Identifiable data or tissue already collected with consent can be retained and used in the study. No further data or tissue should be collected or any other research procedures carried out on or in relation to the participant.

Projected dropout of participants is accounted for in the sample size calculation and therefore withdrawn participants will not be replaced.

6 STUDY ASSESSMENTS

6.1 SCREENING ASSESSMENTS

See section 5.3 for details of screening.

6.2 BASELINE ASSESSMENTS

Patients at *higher-risk* of mid-wall myocardial fibrosis on screening tests will be invited back to attend for baseline assessments, where the following investigations will then take place. At ECG-only sites the screening and baseline assessments may be performed at the same visit.

1. **Relevant medical history**
    - Data on medical history, risk factors and current medication will be collected.

2. **Height and weight**
    - The patient's height and weight will be recorded.

3. **Blood pressure measurement**
    - This should be taken using an appropriately sized arm cuff and performed and recorded three times, with the average of the final two readings used to determine eligibility. If the 1st reading shows severe hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg) the patient should be instructed to lie down in a quiet room for 5 minutes

before the 2nd and 3rd BP measurements are performed.

4. **Urine pregnancy test**
    - This is only required if the participant thinks there is a chance they could be pregnant. Given the age of the study population it is unlikely that this will be required.
5. **Edmonton Frail Scale (EFS)**
    - The Edmonton Frail Scale is a brief, valid and reliable tool for measuring frailty, consisting of nine domains and eleven items.
6. **New York Heart Association Functional Classification**
7. **WHODAS, 12-item version**
8. **Phlebotomy**
    - Approximately 20 ml of venous blood will be taken using standard venepuncture equipment **(optional).** This sample will be spun and processed locally for both serum and plasma then frozen below -70°C for future analysis.
    - In addition, 10ml venous blood will be taken and stored below -70°C for future genetic analysis **(optional)**.
    - Explicit informed consent will be sought for these samples. Provision and/or collection of these samples are optional at both a site and patient level.
    - If a site is acquiring the optional T1 mapping cardiac MRI sequences then a further 4.9ml EDTA sample is required to perform haematocrit measurements. This is required in the calculation of the extracellular volume fraction. This sample should be taken on the same day as the cardiac MRI scan.
9. **Echocardiogram**
    - If a clinical echocardiogram report is available from within the previous 6 months then this result can be used for the trial. If not, a standard transthoracic echocardiogram will be performed. The minimum requirement for reporting is:
        i. Aortic valve peak velocity (continuous wave Doppler)
        ii. Mean aortic valve gradient
        iii. Aortic valve area (calculated using continuity equation)
        iv. An assessment of LV systolic function (visual estimation or Simpson's biplane calculation if available)
10. **Cardiac Magnetic Resonance Imaging**
    - Either a 1.5 or 3 tesla (T) MRI scanner will be used according to local availability at the research site. More details regarding technical aspects of the scan are contained within the standardised cardiac MRI scanning guidance. Sites should ensure that there are no absolute contraindications to cardiac MRI before proceeding.
    - The cardiac MRI will include late gadolinium enhancement imaging, performed 10-15 min following the administration of gadolinium based contrast agent. Full details can be found in the cardiac MRI scanning guidance.

- The cardiac MRI scan will usually take place at the same time as baseline assessment but can take place on a separate visit if necessary. If the optional T1 mapping sequences are being acquired then a plasma EDTA sample is required on the day of the scan to enable calculation of T1 mapping measures.
- Should the cardiac MRI scan be non-diagnostic then it can be repeated at the investigator's discretion.

6.3 FOLLOW UP ASSESSMENT

Participants in Groups A, B and C and participants co-enrolled with EASY-AS will have annual study follow up (linked to the date of randomisation). This will consist of:

1. Annual contact with patient

Participants will be contacted by telephone annually to assess for symptoms or events. At each annual contact NYHA functional classification will be assessed and the WHODAS 2.0 (12-item version) completed. If telephone follow up is unsuccessful, other methods of collecting this information (such as routine clinic appointment, post, email) are acceptable.

Annual follow up by contact with patients will be conducted until 2023. Thereafter remote review patient records with be performed.

Medical record review

Participant medical records should be reviewed at least annually to check for study events that require central reporting, however if research teams become aware of an event it should be reported contemporaneously. The following events should be reported until completion of study follow up:

- Death
- Hospitalisation for syncope, heart failure, chest pain or arrhythmia (ventricular arrhythmia or second or third degree heart block)
- Routine transthoracic echocardiograms
- Stroke
- Insertion of a permanent pacemaker, cardiac resynchronisation therapy device or an automated implantable cardioverter defibrillator
- Endocarditis

2. **Long-term follow up for post-hoc analysis by remote medical record review**

Long-term follow up of participants for the purposes of post-hoc analysis evaluating the risk of earlier re-do aortic valve intervention in participants receiving early intervention will occur via remote medical record review. Participant medical records should be reviewed annually for 10 years post randomisation to check for study events requiring central reporting. The dates and detail of the following events should be recorded:

- Death
- Hospitalisation for syncope, heart failure, chest pain or arrhythmia (ventricular arrhythmia or second or third degree heart block)
- Routine transthoracic echocardiograms
- Stroke
- Insertion of a permanent pacemaker, cardiac resynchronisation therapy device or an automated implantable cardioverter defibrillator
- Endocarditis
- Re-do aortic valve intervention (either surgical aortic valve replacement or transcatheter aortic valve intervention)

- Unplanned hospitalisation due to structural valve degeneration
- Evidence of structural valve degeneration by means of uploading a copy of the echocardiogram and/or CT report

6.4 AORTIC VALVE INTERVENTION

Patients undergoing aortic valve intervention (regardless of treatment group allocation) will have data collected on post-operative complications within 30 days of surgery. This will be achieved by retrospective examination of participant records.

Table 6—1: Schedule of Assessments

	Screening[1]	Baseline	Surgery	Annually
Informed consent - screening[2]	X			
hsTnI	X[3]			
ECG	X[4]			
eGFR	X[5]			
Demographics	X[6]			
Informed consent – study[2]		X		
Relevant medical history		X		
Height and weight		X		
BP measurement		X		
Urine pregnancy test		X[7]		
Edmonton Frail Scale		X		
NYHA classification		X		X
WHODAS 2.0		X		X
Phlebotomy		X		
Echocardiogram		X[8]		
Cardiac MRI		X		
Inclusion/exclusion criteria		X		
Surgery details & post-operative complications			X	
Annual participant contact				X

[1] When screening with ECG only, the screening and baseline assessments may be performed at the same visit
[2] When screening with ECG only, the consent process is simplified to a single consent step
[3] Using Abbott ARCHITECT$_{STAT}$ platform. When screening at ECG only sites, a serum blood sample should be taken and frozen to allow for a retrospective analysis of hsTnI centrally.
[4] If the participant's most recent ECG is within 6 months of screening and is interpretable then there is no requirement to repeat this
[5] If the participant's most recent eGFR result is ≥30 mL/min/1.73 m^2 and within 12 months of screening then there is no requirement to repeat this unless the investigator makes a clinical judgment that a more contemporary result is needed
[6] Demographic data will include a unique identifying number (i.e. CHI or NHS number) for future record linkage
[7] This is only required if the participant thinks there is a chance they could be pregnant.
[8] If the participant's most recent echocardiogram is within 6 months of baseline and the minimum reporting criteria have all been measured then is no requirement to repeat this

Medical record review				X

7 DATA COLLECTION

Data will be collected from consent until final follow up visit. Site-specific source data plans will be created to indicate where protocol required information will be originally documented. Source data worksheets created by the Edinburgh Clinical Trials Unit (ECTU) will be made available but their use is optional.

Study data will be entered onto an eCRF (case report form) developed by ECTU. Data collected as part of the central cardiac MRI review and endpoint adjudication will be entered directly onto the eCRF. The eCRF database will be locked first in early 2024 for an initial data quality check and to allow data field cleaning. A statistical analysis report will be prepared at this point, to check procedures are working, but an unblinded version of this report will only be made available to selected unblinded members of the ECTU statistics team – the trial statistician will not see this report. A second database lock will occur in summer 2024, to allow the final data analysis to be performed and shared with the full trial team.

For the long-term follow up of participants via remote record review, a read-only copy of the eCRF will be created with editable sections for entering the annual data described in section 6.3.3.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

Using a logrank approach with a hazard ratio of 2, we will need to observe 88 primary outcome events to give us 90% power at 5% significance level.

Assumptions prior to study start

We expect the proportion of primary outcome events (all-cause mortality or unplanned AS-related hospitalisation) to be 25% in the routine care arm of the study, and 13.4% in the early intervention arm, over 2 years of follow up (Dweck et al 2011, RBH cohort). We aim to recruit 1000 participants to be screened with cardiac MRI for evidence of LV decompensation (mid-wall fibrosis). We would expect this to result in 400 patients with mid-wall fibrosis being randomised (1:1). We will follow participants up for as long as possible before the end of study, and thus participants will have between 2 and 3.5 years of follow up, and we expect mean follow up to be 2.75 years. We are likely to reach 88 events when we have recruited 356 participants (slightly more allowing for drop-out).

For further calculations we have assumed that our optimal hsTnI threshold will be ~6 ng/L. This is based upon our preliminary troponin data to date, which demonstrated that 62% of patients with an aortic valve peak velocity ≥4.0 m/s had a troponin >6.0 ng/L. Of these patients, 42% had mid-wall fibrosis on cardiac MRI. On this basis, we will therefore need to screen approximately 1600 patients to identify 1000 patients for cardiac MRI in order to recruit our target of 400 patients with mid-wall fibrosis.

At the time that the required amount of data for the primary analysis of the 2 groups with mid-wall fibrosis has accrued, we should have 90% power to detect a difference in the all-cause mortality between the 2 groups who do not receive early surgery of 15% vs 29% (log rank test, p=0.05, 2 sided test)

Protocol v5.0 update

Following a review of recruitment in 2019, it is now anticipated that in order to achieve the target of observing 88 outcome events, the recruitment phase will take approximately 5 years, and therefore participants will have between 2 and 7 years of follow up.

8.2 PROPOSED ANALYSES

The primary outcome is defined as first event of all-cause mortality or unplanned AS-related hospital admission, and the primary comparison will be between patients with midwall fibrosis randomised to early intervention and patients with midwall fibrosis randomised to routine care. Time to primary outcome is defined as time from randomisation to primary outcome. Patients withdrawing consent for their data to be collected prospectively prior to reaching primary outcome will have their time to primary outcome censored at the last contact date. The relationship between intervention and the primary outcome will be analysed using Cox proportional hazard regression adjusted as specified in the separate statistical analysis plan. The results will be expressed as a hazard ratio with the corresponding 95% confidence intervals and 2-sided p-value (which will be considered statistically significant if it is ≤0.05). The individual elements of the composite primary outcome will be reported separately. There are no planned subgroup analyses.

Secondary outcomes will be analysed using appropriate methods: Cox proportional hazards regression for time-to-event outcomes, logistic regression for binary outcomes and linear regression for normally distributed continuous outcomes, adjusted as described above. Continuous outcomes that are not normally distributed will be analysed using appropriate nonparametric techniques. Secondary outcomes will be presented for 3 groups: patients randomised to early intervention with midwall fibrosis; patients randomised to routine care with midwall fibrosis; and patients randomised to routine care without midwall fibrosis. A first set of secondary analyses will compare patients with midwall fibrosis randomised to early intervention and patients with midwall fibrosis randomised to routine care, and a second set of secondary analyses will compare patients randomised to routine care with midwall fibrosis and patients randomised to routine care without midwall fibrosis.

For the purpose of analysis, we will retain participants in the treatment groups to which they were originally assigned irrespective of the treatment actually received. Every effort will be made to minimise missing data, analysis will be a complete case analysis. If there is a sufficient level of missing data for it to affect our conclusions, a multiple imputation analysis will be undertaken, using clinically appropriate variables, as a sensitivity analysis. A full statistical analysis plan will be written during the trial, and finalised prior to database lock.

Statistical analysis of the long-term post-hoc follow-up data recorded following the second database lock will be conducted by the clinical research team. Cox proportional hazards regression will be used for analysis of time-to-event outcomes. Every effort will be made to minimise loss to follow up, but a space for recording such events will be created in the eCRF.

9 ADVERSE EVENTS

The Investigator, or a delegated researcher, is responsible for the detection and documentation of adverse events that may be related to participating in the study and that meet the criteria and definitions detailed below.

9.1 DEFINITIONS

An **adverse event** (AE) is an untoward medical occurrence in a study participant.

An **adverse reaction** (AR), in the context of this study, is any untoward and unintended response which is related to any dose of gadolinium based contrast agent administered to that participant.

A **serious adverse reaction** (SAR) is any AR that:

- results in death of the clinical trial participant; is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

A **suspected unexpected serious adverse reaction** (SUSAR) is any AR that is classified as serious and is suspected to be caused by the gadolinium contrast agent, that it is not consistent with the information in the Summary of Product Characteristics (SPC).

*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to randomisation will not meet the seriousness criteria. Any hospitalisation that is planned post randomisation will meet the seriousness criteria unless it does not constitute an untoward medical occurrence (e.g. cosmetic elective surgery, social and/or convenience admission, etc.).

9.2 IDENTIFYING AEs AND ARs

ARs will be recorded from the time a participant signs the consent form until their scanning is complete

AEs (outcome measures) will be identified from the time a participant signs the consent form to take part in the study until the end of study.

9.3 RECORDING AEs AND ARs

AEs, including post-operative complications, potential aortic stenosis related hospitalisations, and mortality, will be recorded as part of the outcome measures in the study CRF. There is no requirement to complete an additional AE form.

When an AE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. To the extent the CRF permits, the Investigator will record relevant safety information in the CRF.

Any adverse reaction (AR) to gadolinium contrast that meets seriousness criteria (see section 9.1) will be recorded and reported in the study CRF and will also be recorded on an ACCORD SAE form, which will then be sent to the Sponsor via email (safety@accord.scot).

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as AEs/ARs if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of underlying disease should not be recorded as adverse events.

9.4 ASSESSMENT OF AEs, SAEs, ARs, SARs and SUSARs

Seriousness, causality, severity and expectedness will be assessed by the PI.

The Investigator is responsible for assessing each adverse event. The CI may not downgrade an event that has been assessed by an Investigator as a SAR or SUSAR, but can upgrade an AR to a SAR or SUSAR if appropriate.

9.4.1 Assessment of Causality

The Investigator will make an assessment of whether an AE is likely to be related to the administration of gadolinium (and therefore be considered an AR) according to the definitions below.

- Unrelated: Where an event is not considered to be related to the administration of gadolinium.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the administration of gadolinium in this study.

9.4.2 Assessment of Seriousness

Subsequent to the assessment causality, the Investigator will make an assessment of seriousness as defined in Section 9.1.

9.4.3 Assessment of Severity

The Investigator will make an assessment of severity for each SAR, and record this on the ACCORD SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

9.4.4 Assessment of Expectedness of SARs

The Investigator will make an assessment of expectedness of any SARs identified following gadolinium administration. The assessment will be based upon the reference safety information available in the most current version of the Summary of Product Characteristics (SPC) for the gadolinium-based contrast agent dosed.

9.5 REPORTING OF SARs/SUSARs

As this trial is a non-CTIMP and involves procedures and interventions that are very well established in the medical community, with extensive information available regarding risks, only serious adverse reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) related to Gadolinium administration, will be onward reported to the Sponsor.

Once the Investigator becomes aware that a gadolinium related SAR/SUSAR, has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office within 24 hours. If the Investigator does not have all information regarding an event, they should not wait for this additional information before notifying ACCORD. The ACCORD SAE report form will be used to submit the event report, and can be updated when the additional information is received.

The SAE form will be transmitted by fax to ACCORD on +44 (0)131 242 9447 or may be submitted by hand to the office or sent via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File.

9.6 REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The Trial Manager will provide the ACCORD Research Governance & QA Office with quarterly safety reports based on the data collected on the CRF until the second database lock.

9.7 FOLLOW-UP PROCEDURES

After initially reporting a gadolinium related SAR/SUSAR, the Investigator will follow each participant until resolution or the completion of study follow-up. Follow-up information will be reported to the ACCORD office.

10 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 TRIAL MANAGEMENT GROUP

ECTU will be responsible for trial management including: organisation of management group meetings, organisation of the steering committee, contracting with other organisations, preparation of REC and R&D applications, standard operating procedures, provision of the randomisation system, database development, data management. Data analysis will be performed by ECTU and/or the Edinburgh Clinical Research Facility.

The trial will be led by the Trial Management Team coordinated by ECTU. An informal project management group (PMG) comprising the Chief Investigator, Research Fellow and relevant members of the ECTU team will be formed. The Academic and Clinical Central Office for Research & Development (ACCORD) in Edinburgh will provide Sponsorship and monitoring oversight for the project and the trial will be conducted in line with the relevant Sponsor SOPs which are available on the Sponsor website.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

10.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the study. The terms of reference of the Trial Steering Committee, and the names and contact details are detailed in the TSC charter.

10.3 DATA MONITORING COMMITTEE

As this trial involves procedures and interventions that are very well established in the medical community, with extensive information available regarding risks, it was felt that a Data Monitoring Committee is not required.

10.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor and REC review. In the event of an audit or

monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation.

10.5 ENDPOINT ADJUDICATION

Two investigators who are blinded to randomisation details will be asked to independently adjudicate AS-related hospitalisation events from a review of the medical records (relevant sections of the medical records will be anonymized and uploaded to the study database). In the event of disagreement, the opinion of a third reviewer will be sought. Causes of death will be established from the death certificate.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

11.2 INVESTIGATOR RESPONSIBILITIES

The PI is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the PI. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document, with the original filed in the Investigator Site File (ISF) and a copy in the participant's medical notes.

11.2.2 Study Site Staff

The Investigator must be familiar with the intervention, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with

the study are adequately informed about the intervention, protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

11.2.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

11.2.5 GCP Training

All members of staff involved in study specific activities are strongly encouraged to undertake GCP training in order to understand the principles of GCP.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where it does not identify individuals and re-identification is not likely to take place.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Sponsor every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot.

12.3 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point for sites continuing to long-term remote follow up or from receiving Final Close Out Letter for sites not continuing to long-term remote follow up. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor. Sites not continuing to long-term remote follow up will have collected scheduled annual follow ups up for active participants until 31st October 2023 and are not expected to implement Substantial Amendment 04 (AM13) where protocol v6.0 first details the long-term remote follow up.

12.4 END OF STUDY

The end of study is defined as the last patient's last remote medical review, up to 10 years post randomisation.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.5 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

- The following arrangements are in place to fulfil the co-sponsors' responsibilities:
- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by

poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

The protocol for this trial will be submitted for publication and the trial results will be submitted for publication even if this trial stops early. If successfully completed the main paper from this project will be submitted for publication in a leading international general medical journal.

The main outputs will be provided to guideline developing bodies (including NICE, SIGN and the European Society of Cardiology), key professional organisations (such as the College of Emergency Medicine) and patient representative organisations (such as the British Heart Foundation).

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared in accordance with the funders requirements. The authors for this project are listed in the trial's writing committee and publication policy document.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their centres (where appropriate and according to their discretion).

13.3 REPRODUCIBLE RESEARCH AND DATA SHARING

Following publication of the primary paper, a deidentified individual participant data set will be submitted to a data archive for sharing purposes. Access to the deidentified dataset will be under a controlled access model in line with ECTU or University of Edinburgh policies at that time.

14 REFERENCES

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APPENDIX A

Post-aortic valve intervention complications secondary endpoint

The following post aortic valve intervention complications should be recorded if they occur within 30 days of surgery:

- Death caused by an immediate complication of aortic valve intervention
- Reoperation for any reason (e.g. redo valve replacement, pericardial collection)
- Stroke
- Myocardial infarction
- Diagnosis of infective endocarditis
- Severe paravalvular regurgitation
- Valve thrombosis requiring treatment
- Major vascular complication
    - Access site injury leading to life-threatening bleeding, visceral ischaemia or neurological impairment
- Life threatening bleeding
    - Bleeding in a critical organ (e.g. intracranial, intraspinal, intraocular or intrapericardial requiring treatment)
    - Bleeding causing hypovolaemic shock
    - Drop in haemoglobin >5g/dL or ≥4 units blood transfused
- Wound dehiscence
- Permanent pacemaker implantation
- Still requiring renal replacement therapy at 30 days post surgery

APPENDIX B

Definition of Sudden Cardiac Death

Death that occurs unexpectedly and not within 30 days of an acute myocardial infarction (MI).

Note: Sudden cardiac death includes the following scenarios:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 min of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic recording, witnessed on a monitor, or unwitnessed but found on ICD review)
- Death after unsuccessful resuscitation from cardiac arrest (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac aetiology
- Unwitnessed death in a subject seen alive and clinically stable 24 hours before being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the patient's clinical status preceding death should be provided if available)
- Unless additional information suggests an alternate specific cause of death, if a patient is seen alive 24 hours before being found dead, *sudden cardiac death* should be recorded. For patients who were not observed alive within 24 hours of death, sudden cardiac death should not be recorded. (e.g., a subject found dead in bed but who had not been seen by family members for >24 h).

Adapted from Hicks, K. A. et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Journal of the American College of Cardiology ***66,*** *403–469 (2015).*