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The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Trial

A multicentre randomised controlled trial to assess the clinical effectiveness and cost-utility of TAVI, compared with conventional surgical aortic valve replacement (AVR) in patients with severe symptomatic aortic stenosis at intermediate or high operative risk.

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1 SYNOPSIS

Study title	The UK Transcatheter Aortic Valve Implantation (UK TAVI) Trial
Sponsor	University of Leicester
Primary objective	To assess the clinical effectiveness and cost-utility of transcatheter aortic valve implantation (TAVI) as an alternative to conventional surgical aortic valve replacement (AVR) in patients with severe symptomatic aortic stenosis who are at intermediate or high operative risk.
Secondary objectives	To identify predictors of procedure-related morbidity and mortality in patients undergoing surgical AVR or TAVI to guide the pre-procedural evaluation of patients requiring intervention and to inform the future development of improved risk-assessment tools.
Study hypothesis	The primary study hypothesis is that TAVI is non-inferior to surgical AVR in respect of the primary endpoint at one year
Trial design	Pragmatic, open-label, parallel group, non-inferiority, randomised controlled, phase III trial. Participants will be randomised 1:1 to receive either AVR or TAVI.
Trial participants	Patients aged ≥70 years with severe symptomatic aortic stenosis at intermediate or high operative risk
Planned sample size	It is intended to enrol 808 patients. Interim review of the planned sample size will be undertaken by the independent Data Monitoring Committee.
Eligibility criteria	<u>Participants must meet ALL of the following criteria:</u> • Severe symptomatic aortic stenosis referred for intervention; • Age ≥80 years; or Age ≥70 years with intermediate or high operative risk from conventional AVR, as determined by the MDT; • Both conventional AVR and TAVI deemed to be acceptable treatment options; • Participant able and willing to give written informed consent; • Participant able (in the Investigator's opinion) and willing to comply with all study requirements.

	<u>Subjects may not enter the study if ANY of the following apply:</u> • Intervention deemed inappropriate due to co-morbidity or frailty; • Life expectancy less than one year due to co-morbidity; • Previous AVR or TAVI; • Technically unsuitable for either AVR or TAVI; • Concomitant coronary artery disease requiring revascularisation for which only surgery is considered appropriate; • Predominant aortic regurgitation (AR); • Severe mitral regurgitation (MR) or likely need for concomitant surgery or cardiac intervention other than planned coronary artery surgery or percutaneous coronary intervention (PCI) as part of treatment strategy.
Investigational treatment	Transcatheter aortic valve implantation (TAVI) using any clinically appropriate CE-marked device with proven efficacy and safety
Comparator	Conventional surgical aortic valve implantation (AVR)
Minimum follow-up	Five years
Primary endpoint	All-cause mortality at one year
Secondary outcomes	• All-cause mortality at 30 days, 2, 3, 4 and 5 years • Cardiovascular mortality at 30 days and annually to 5 years • Quality-adjusted survival at 3 months and annually to 5 years • Stroke at 30 days and annually to 5 years • Re-intervention at 30 days and annually to 5 years • Death from any cause or stroke at 30 days and annually to 5 years • Death from any cause or disabling stroke at 30 days and annually to 5 years • Death from any cause, stroke or re-intervention at 30 days and annually to 5 years • Quality of life (Minnesota Living With Heart Failure Questionnaire at 6 weeks and one year; EQ-5D-5L at 2 weeks, 6 weeks, 3 months, 6 months, and annually to 5 years) • Symptoms and functional capacity (CCS scale and NYHA class at 6 weeks, 3 months, 6 months and annually to 5 years; Nottingham EADL and 6-min walk at 6 weeks and one year)

	• Cognitive function (Mini-Mental-State-Index at 6 weeks and one year) • Procedural success and in-hospital complications • Duration of post-procedural hospital stay • Vascular complications at 30 days and one year • Major bleeding at 30 days and one year • Infective endocarditis at 30 days and annually to 5 years • Myocardial infarction at 30 days and annually to 5 years • Conduction disturbance requiring permanent cardiac pacing pre-discharge and at one year • Renal replacement therapy at 30 days and one year • Echocardiographic measures (left ventricular ejection fraction, mass, dimensions and volumes; aortic regurgitation; aortic valve gradient and area, at 6 weeks and one year) • Costs, cost-utility and incremental cost-effectiveness ratio at 1 year, 5 years and estimated over lifetime using an extrapolation model
End of trial definition	Date of last visit or telephone follow-up of the last recruited participant
Study timelines	Total 9 years: 6 months set-up; 3 years recruitment; 5 years follow-up; 6 months close-out
Statistical methods	The primary analysis will use an intention-to-treat approach, with inclusion of all randomised participants. Time-to-event outcomes (mortality, stroke, re-intervention) and length of hospital stay will be analysed using survival analysis techniques to allow for censoring and differential follow-up, including Cox proportional hazards regression models to adjust for potential confounders and imbalances in baseline covariates. Categorical and ordinal outcomes (e.g. symptoms and functional capacity) will be analysed using Chi-squared tests and logistic (ordinal) regression to allow for potential confounders and imbalances in baseline covariates. Continuous outcomes (including echocardiographic measures) will be analysed using parametric and non-parametric tests, as appropriate. Quality of life data will be analysed using quality-adjusted survival methods to allow for mortality and censoring. Sub-group analyses will be undertaken for a number of pre-specified sub-groups (including age, pre-operative risk score,

	frailty, left ventricular function, concurrent or proximate coronary artery revascularisation, pre-specified intention to revascularise if assigned to receive surgical AVR, and specified comorbidities).

2 ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AR	Aortic regurgitation
AVR	Aortic Valve Replacement
BCIS	British Cardiovascular Intervention Society
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass grafting
CI	Chief Investigator
CRF	Case Report Form
CW	Continuous wave
DMC	Data Monitoring Committee
EF	Ejection fraction
FS	Fractional shortening
GCP	Good Clinical Practice
GP	General Practitioner
HEHTA	Health Economics and Health Technology Assessment group, University of Glasgow
HERC	Health Economics Research Centre, University of Oxford
ICH	International Conference of Harmonisation
ICMJE	International Committee of Medical Journal Editors
IVC	Inferior vena cava
LA	Left atrial
LV	Left ventricular
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MR	Mitral regurgitation
mRS	Modified Rankin Scale

PA	Pulmonary artery
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PISA	Proximal isovelocity surface area
PSSRU	Personal Social Services Resource Unit
PTCA	Percutaneous Transluminal Coronary Angioplasty
PW	Pulsed wave
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RPS	Right parasternal
RV	Right ventricular
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAR	Serious Adverse Reaction
SCTS	Society for Cardiothoracic Surgery in Great Britain & Ireland
SOP	Standard Operating Procedure
SS	Suprasternal
SUSAR	Suspected Unexpected Serious Adverse Reactions
TAPSE	Tricuspid annular plane systolic excursion
TAVI	Transcatheter Aortic Valve Implantation
TIA	Transient Ischaemic Attack
TR	Tricuspid regurgitation
TSC	Trial Steering Committee
USADE	Unanticipated Serious Adverse Device Effect
VARC	Vascular Academic Research Consortium

3 BACKGROUND AND RATIONALE

3.1 Aortic Stenosis

Aortic stenosis is the most common form of valvular heart disease in the Western world. It is predominantly a disease of the elderly, in whom it results from a degenerative process against a background of atherosclerosis. The estimated prevalence is 2.8% in people over the age of 75 years and 4% in those over 80 years. Narrowing and calcification of the aortic valve causes obstruction to the outflow of blood from the heart. When narrowing becomes severe, with a high pressure gradient across the valve, symptoms such as angina, breathlessness and syncope, and heart failure commonly ensue and are associated with an abrupt and marked decline in survival. Average survival in untreated patients after the onset of symptoms is less than 2-3 years, with a high risk of sudden death.

3.2 Surgical Aortic Valve Replacement

The only effective conventional treatment for severe aortic stenosis is surgical replacement of the aortic valve (AVR). Approximately 7,250 AVR procedures were performed in the UK in 2008, the majority (>90%) being for patients with aortic stenosis and almost 40% in patients aged over 75 years.[2] Surgical AVR involves open chest surgery with cardiopulmonary bypass but the procedure is now well-established and results are excellent, with in-hospital mortality of 2.5% overall for isolated AVR and 5.8% in patients over 80 years of age. For patients undergoing concomitant coronary artery bypass grafting (CABG), the corresponding figures are 4.5% and 9% respectively.[2]

Although there have been no randomised trials of surgery, there is good evidence that it relieves symptoms, improves functional capacity and quality of life, and reduces morbidity and mortality. Age alone should not be a deterrent to surgery, as survival after successful AVR in patients aged 65 years or older is only marginally lower than that observed in age and gender matched people in the general population. However, the elderly population often have multiple co-morbid conditions, which may increase operative risk, complicate post-operative recovery and independently influence subsequent morbidity and mortality even after successful surgery. One-year post-operative mortality in patients over 80 years of age is 13% for isolated AVR and 18% for AVR with CABG.[2] Although the total number of AVR procedures and the proportion

of operated patients who are older or at high operative risk is increasing, there is evidence that around one-third of elderly patients with severe aortic stenosis are not offered surgery.[3]

3.3 Transcatheter Aortic Valve Implantation (TAVI)

The recent development of Transcatheter Aortic Valve Implantation (TAVI), which avoids the need for open-chest surgery, has offered a less invasive alternative to AVR in patients at high operative risk.[4] Surgical valve replacement in these patients may be complicated not only by increased mortality but also by a prolonged stay in the intensive care unit and surgical ward, with consequent cost implications for the NHS. These adverse outcomes might be attenuated by TAVI. The procedure may also be of value in those for whom AVR is not an option, who have intractable symptoms, impaired quality of life and poor survival, with a high degree of dependency and increased use of health care resources.

3.3.1 Non-randomised data

The first human TAVI implant was in 2002, since when over 50,000 procedures have been performed worldwide, including over 3,000 in the UK. Outcome data from case series and registries confirm high procedural success rates, with evidence of a learning curve (e.g. initial success of 78%, rising to 96% after 25 implants). Early haemodynamic improvement, relief of symptoms and improved functional capacity and quality of life appear to be comparable to that achieved with conventional AVR. In preliminary case series, mortality at 30 days and one year was around 10% and 30% respectively but the case-mix included patients deemed unsuitable for surgery, as well as those who were operable but at increased peri-operative risk, the latter group being the target population for the randomised clinical trial (RCT) described in this protocol. It is likely that much of the late mortality is related to co-morbidity, rather than to the procedure or underlying valve disease. Recently, outcomes of patients treated in the UK between 2007 and 2009 have been reported from the UK TAVI Registry.[5] The 30-day mortality was 7.1% with a one-year survival of 78.6%. These data, in common with those from other reported case series,[6,7] include patients who were often at very high risk and unsuitable for conventional AVR. Comparability with surgical outcome data is thus limited. There is likely to be selection bias in the surgical data, with those patients in whom better outcomes were anticipated being more likely to have been operated upon. In contrast, the UK TAVI trial will compare TAVI and AVR in well-matched patients for whom either treatment option is considered feasible and appropriate. It will

assess the presumed short-term advantages of TAVI and clarify whether medium and long-term durability and function of the valve are at least as good as for surgical AVR.

3.3.2 The PARTNER trial

The PARTNER trial was the first major RCT of TAVI. It comprised two discrete cohorts. PARTNER B enrolled 358 high-risk patients with severe symptomatic aortic stenosis, who were not considered suitable for surgery due to coexisting conditions associated with a predicted 30-day operative mortality (or risk of serious irreversible complications) of 50% or higher.[8] Patients were randomly assigned to either TAVI or standard therapy (medical treatment ± balloon aortic valvuloplasty). Thirty-day mortality was 5.0% in the TAVI group and 2.8% in the standard therapy group (p=0.41). At one year, all-cause mortality (the primary outcome) was 30.7% with TAVI, compared with 50.7% with standard therapy (hazard ratio 0.55; 95% CI 0.40 to 0.74). In addition, in the TAVI group, the repeat hospitalisation rate was halved, symptoms amongst the survivors were greatly reduced, 6-minute walk distance increased significantly and quality of life was improved.[9] Major stroke was more common with TAVI than with standard therapy at 30 days (5.0% *vs* 1.1%; p=0.06) and one year (7.8% *vs* 3.9%; p0.18). These results suggest an important role for TAVI in selected high-risk patients who are unsuitable for surgery.

Of more direct relevance to the current study is PARTNER A, which was designed to assess whether TAVI is non-inferior to surgical AVR in patients at high operative risk.[10] In total, 699 patients with severe symptomatic aortic stenosis were enrolled, all of whom were deemed suitable for surgical AVR but at high operative risk on the basis of co-existing conditions, with a predicted risk of death at 30 days of at least 15% and a minimum STS score of 10%. Patients were assessed to determine whether they were suitable for transfemoral TAVI (n=492) or required a transapical approach (n=207) and each group was then randomly assigned to receive TAVI or surgical AVR. Thirty-day mortality was 3.4% in the TAVI group and 6.5% in the surgical group (p=0.07) on the basis of *intention-to-treat*. Forty-two patients did not receive the assigned procedure (4 in the TAVI group and 38 in the surgical group) and 30-day mortality in an *as-treated* analysis was 5.2% and 8.0% for TAVI and surgical AVR respectively (p=0.15). At one year, all-cause mortality on the basis of *intention-to-treat* (the primary outcome) was 24.2% in the TAVI group, compared with 26.8% in the surgical group (p=0.44), the difference of -2.6% (two-sided 95% CI -9.3 to 4.1; upper limit of the one-sided 95% CI 3.0) being within the pre-specified non-inferiority margin of 7.5% (p=0.001 for non-

inferiority). Early symptom reduction favoured TAVI but at one-year both groups had similar and significant improvements in cardiac symptoms and 6-minute walk distance. Quality of life also improved sooner after TAVI but improvements were similar for the two groups at 6 and 12 months.[11] The TAVI group had a shorter length of hospital stay than the surgical group (8 *vs* 12 days) and less time in intensive care (3 *vs* 5 days). Major stroke was more common with TAVI than with surgery at 30 days (3.8 *vs* 2.1%; p=0.20) and one year (5.1 *vs* 2.4%; p=0.07). At 30 days, major vascular complications were more common with TAVI than with surgery (11.0 *vs* 3.2%; p<0.001) but there was a lower incidence of major bleeding complications (9.3 *vs* 19.5%; p<0.001). Two-year results from PARTNER A have subsequently been published.[12] These showed all-cause mortality of 33.9% in the TAVI group and 35.0% in the surgical group, based on Kaplan-Meier analysis (p=0.78). The early increase in the risk of stroke after TAVI was attenuated with longer follow-up and the frequency of any stroke at two years did not differ significantly between the groups (hazard ratio 1.22; 95% CI, 0.67 to 2.23; p=0.52). Paravalvular regurgitation was more frequent after TAVI and even mild paravalvular regurgitation was associated with increased late mortality.

The preliminary results from PARTNER A are extremely encouraging but annual follow-up is scheduled to continue for a minimum of 5 years and it will be essential to confirm the long-term durability of TAVI implants and sustained clinical benefit over this period and beyond before a role for TAVI as an alternative to surgical AVR in operable patients can be justified. There are clear short-term advantages of TAVI but it is not yet clear that it can match the excellent long-term results of surgical AVR. The National Institute for Health and Clinical Excellence (NICE) issued preliminary guidance on the use of TAVI in June 2008.[13] This recognised the limited evidence of long-term efficacy of TAVI and advised its use only with special arrangements for audit or research. NICE has subsequently reconsidered TAVI in the light of data from the PARTNER trial and issued updated guidance in March 2012.[14] This recommended that for patients considered unsuitable for surgical AVR, TAVI may be used with normal arrangements for clinical governance, consent and audit. However, for patients for whom surgical AVR is considered suitable, whether at high operative risk or not, the evidence on the efficacy of TAVI was deemed to be inadequate and it was recommended that it only be used in the context of research. The guidance specifically recommends the enrolment of suitable patients into the UK TAVI trial.

3.3.3 The UK TAVI trial

The UK TAVI has some similarity in design to the PARTNER A trial but there are several key aspects that make it distinct and of continuing relevance:

- **The patient population to be enrolled in UK TAVI will encompass a broader spectrum of risk, with the inclusion of patients at intermediate as well as high risk.** Inclusion in PARTNER A required anticipated 30-day mortality of at least 15% and a minimum STS score of 10%. In PARTNER A, the mean STS score was 11.8% and the mean Logistic EuroSCORE (LES) was 29.3%. By contrast, patients included in the UK TAVI registry (2007-2009), reflecting actual UK practice in a mixture of operable and non-operable patients, had a median LES of 18.5%. This confirms that there is already a shift to the consideration of TAVI in lower risk patients ("indication creep") and it is essential that the relative safety and efficacy of TAVI compared with surgery are evaluated in an RCT to validate this approach in operable patients before it becomes established clinical practice without adequate supportive evidence.

- **UK TAVI is a generic trial that will uniquely include multiple TAVI technologies.** In PARTNER, all patients received an early version of the Edwards Sapien™ valve, the trial being sponsored by the manufacturer. This is important, as the optimal TAVI technology and approach in a given patient are often anatomically determined and the different devices are thus complementary.[15] Furthermore, in addition to the three currently CE-marked devices in widespread use, newer valves that are CE-marked and come to market during the recruitment period may also be included subject to sufficient and satisfactory preliminary outcome data. This approach is only possible in a publicly funded trial. All other previous and planned trials have been funded by industry, with an inevitable influence on trial design and exposure to potential conflicts of interest.

- **UK TAVI will include patients with coronary artery disease for which revascularisation is felt to be appropriate, in contrast to PARTNER, from which such patients were excluded.** About 48% of patients currently receiving TAVI have significant coronary artery disease and 42% of patients having surgical AVR undergo concurrent revascularisation. There are currently no data comparing percutaneous and surgical approaches to the management of this common clinical scenario.

The UK TAVI trial will complement PARTNER and other planned trials. For a new and disruptive technology, such as TAVI, a single RCT with the limitations of PARTNER will not be sufficient to define its place in clinical practice. The remarkably good outcomes in PARTNER are a testament to the skill of the investigators in patient selection, operative technique and peri-operative management. However, the surprisingly low 30-day mortality of 3.4% in Cohort A and 5.0% in Cohort B, compared with 7.1% in the UK TAVI registry and similar or higher figures from other European registries, inevitably raises questions about the generalisability of the findings. The figures are even more remarkable in view of the fact that the trial included centres that commenced enrolment whilst still at the start of their learning curve for TAVI, when complications would be expected to be at their highest (only two prior proctored implants were required for a centre to participate). There is also uncertainty as to whether the early vascular complication and stroke rate with TAVI will be lower with the use of newer technologies, comprising smaller calibre devices and delivery systems, than with the early generation technology used in PARTNER. This could have a major impact on clinical outcomes and cost-effectiveness. The UK setting of the UK TAVI trial will generate clinical and cost outcome data that will relate to and directly inform NHS practice and guidelines.

The UK TAVI trial will also provide an opportunity to identify predictors of procedure-related morbidity and mortality in patients undergoing surgical AVR or TAVI that will subsequently inform the pre-procedural evaluation of patients requiring intervention. They may also help with the future development of better procedure-specific tools to predict surgical risk than those currently available. Until recently, the most commonly used risk score in the UK was the Logistic EuroSCORE.[16] This was not devised specifically for AVR patients and overestimated the surgical risk approximately twofold.[17,18] The STS score[19] has been shown to perform better than the EuroSCORE in the context of high-risk surgical AVR but also tends to overestimate risk to some extent.[20] The EuroSCORE has recently been revised and superseded by the EuroSCORE II.[21,22] This performs better than its predecessor but remains imperfect, particularly at higher levels of risk.[23] A particular shortcoming of the currently available risk prediction tools is that they do not incorporate any measure of frailty, which may be an important determinant of procedural and post-procedural outcomes. An assessment of frailty will therefore be included in the pre-procedural assessment of all patients undergoing intervention in the study.

The trial design has been developed in collaboration with the Specialised Commissioning Groups and closely reflects the evaluative programme advocated in the Commissioning Framework that was published to guide the implementation of TAVI in the UK.[24] Consequently, the majority of the regional Specialised Commissioning Groups have agreed to recommend funding of treatment costs within the trial. The trial design accords with position statements of the European Association of Cardiothoracic Surgery and the European Society of Cardiology,[4] and the British Cardiovascular Intervention Society (BCIS) and the Society for Cardiothoracic Surgery (SCTS).[25] The need for the trial is endorsed by NICE interventional procedure guidance 421 (March 2012), which explicitly recommends that clinicians consider entering suitable patients into the trial.[14]

4 OBJECTIVES

4.1 Primary Objective

To assess the clinical effectiveness and cost-utility of transcatheter aortic valve implantation (TAVI) as an alternative to conventional surgical aortic valve replacement (AVR) in patients with severe symptomatic aortic stenosis who are at intermediate or high operative risk.

4.2 Secondary Objective

To identify predictors of procedure-related morbidity and mortality in patients undergoing surgical AVR or TAVI to guide the pre-procedural evaluation of patients requiring intervention and to inform the future development of improved risk-assessment tools.

5 TRIAL DESIGN

5.1 Summary of Trial Design

The UK TAVI Trial is a prospective, multi-centre, parallel group, pragmatic, non-inferiority, randomised controlled trial to assess the clinical effectiveness and cost-utility of TAVI, compared with conventional surgical aortic valve replacement, in patients with severe symptomatic aortic stenosis, who are at intermediate or high operative risk. Participants will be randomly assigned (1:1) to receive either TAVI or conventional surgical AVR. The study is open-label but with outcome assessment adjudicated by an independent Events Committee blinded to treatment assigned whenever possible. The

trial aims to enrol 808 patients, with minimum follow-up of one year in the first instance. Long-term follow-up to 5 years will subsequently be undertaken. The overall study design is summarised in Appendix A.

5.2 Primary and Secondary Endpoints/ Outcome Measures

5.2.1 Primary endpoint

The primary endpoint for the study will be all-cause mortality at one year

5.2.2 Secondary outcome measures

- All-cause mortality at 30 days, 2, 3, 4 and 5 years
- Cardiovascular mortality at 30 days and annually to 5 years
- Quality-adjusted survival at 3 months and annually to 5 years
- Stroke at 30 days and annually to 5 years
- Re-intervention at 30 days and annually to 5 years
- Death from any cause or stroke at 30 days and annually to 5 years
- Death from any cause or disabling stroke at 30 days and annually to 5 years
- Death from any cause, stroke or re-intervention at 30 days and annually to 5 years
- Quality of life (Minnesota Living With Heart Failure Questionnaire at 6 weeks and one year; EQ-5D-5L at 2 weeks, 6 weeks, 3 months, 6 months, and annually to 5 years)
- Symptoms and functional capacity (CCS scale and NYHA class at 6 weeks, 3 months, 6 months and annually to 5 years; Nottingham EADL and 6-min walk at 6 weeks and one year)
- Cognitive function (Mini-Mental-State-Index at 6 weeks and one year)
- Procedural success and in-hospital complications
- Duration of post-procedural hospital stay
- Vascular complications at 30 days and one year
- Major bleeding at 30 days and one year
- Infective endocarditis at 30 days and annually to 5 years
- Myocardial infarction at 30 days and annually to 5 years
- Conduction disturbance requiring permanent cardiac pacing pre-discharge and at one year
- Renal replacement therapy at 30 days and one year

- Echocardiographic measures (left ventricular ejection fraction, mass, dimensions and volumes; aortic regurgitation; aortic valve gradient and area, at 6 weeks and one year)
- Costs, cost-utility and incremental cost-effectiveness ratio at 1 year, 5 years and estimated over lifetime using an extrapolation model

Definitions of cardiovascular events and other key clinical outcomes will be aligned with those developed and published by the Valve Academic Research Consortium (VARC),[26,27] which are summarised in Appendix B. The use of these standard outcome definitions will facilitate subsequent meta-analysis of individual patient data with those from other trials.

5.2.3 Health economic analysis

An economic evaluation will be conducted alongside the proposed trial. The main objectives will be to make a robust estimate of the cost-effectiveness of TAVI as an alternative to AVR, with outcomes measured in terms of quality-adjusted life years.

The analysis will include detailed information on the resource use and costs associated with the TAVI procedure (trans-arterial or trans-apical), including devices and consumables, staff, procedure time, recovery time, complications and failures. Subsequent hospital stay and hospital readmissions will be included. Resource use data will be collected primarily from trial record forms, and NHS and GP databases, supplemented with a simple (one-page) patient resource-use questionnaire to be completed at baseline and at the annual assessments. The EuroQol EQ-5D-5L will also be administered prior to intervention and during follow-up at 2 weeks, 6 weeks, 3 months, 6 months, 12 months and annually thereafter, and will be the primary method of making estimates of quality-adjusted survival.

Unit costs for resources used will be obtained from national sources, including NHS reference costs and the Personal Social Services Resource Unit (PSSRU), supplemented with information from manufacturers and a small sample of participating centres on the cost of devices. Accurate estimates of the cost of the procedure will inform the cost-effectiveness analysis and will also be helpful in assessing a realistic tariff price for the procedure.

Cost per QALY gained will be estimated at one-year and 5-year follow-up and then extrapolated to a lifetime using trial data in a Markov model that will be developed collaboratively between the Health Economics Research Centre (HERC) at the University of Oxford and the Health Economics and Health Technology Assessment group (HEHTA) at the University of Glasgow. The model will be based on one that has previously been developed by HEHTA using registry information and published literature. This will allow full probabilistic sensitivity analyses to be conducted and reported.

The modelling will also assess the cost-effectiveness of selecting patients using a risk-prediction model developed as part of the study, and in particular will assess cost-effectiveness at different risk-prediction thresholds.

5.3 Trial Participants

5.3.1 Inclusion criteria

Participants must meet ALL of the following criteria:

- Severe symptomatic aortic stenosis referred for intervention;
- Age ≥80 years;
  or
  Age ≥70 years with intermediate or high operative risk from conventional AVR, as determined by the MDT;
- Both conventional AVR and TAVI deemed to be acceptable treatment options;
- Participant able and willing to give written informed consent;
- Participant able (in the Investigator's opinion) and willing to comply with all study requirements.

5.3.2 Exclusion criteria

Subjects may not enter the study if ANY of the following apply:

- Intervention deemed inappropriate due to co-morbidity or frailty;
- Life expectancy less than one year due to co-morbidity;
- Previous AVR or TAVI;
- Technically unsuitable for either AVR or TAVI;
- Concomitant coronary artery disease requiring revascularisation for which only surgery is considered appropriate;
- Predominant aortic regurgitation (AR);

- Severe mitral regurgitation (MR) or likely need for concomitant surgery or cardiac intervention other than planned coronary artery surgery or percutaneous coronary intervention (PCI) as part of treatment strategy.

5.4 Participant Expenses and Benefits

Participants will not be remunerated in any way for their involvement in the trial. Reasonable travel expenses for any visits additional to normal care will be reimbursed by the enrolling site on production of receipts or a mileage allowance may be provided, as appropriate.

5.5 Study Procedures

5.5.1 Informed consent

The participant must personally sign and date the latest approved version of the consent form before any study specific procedures are performed. The patient information sheet will be presented to the participants, detailing the exact nature of the study, the requirements of the protocol and the known complications of TAVI and surgical AVR. The risks and benefits of the two treatment options will be fully explained. In particular, the uncertain medium to long-term results after TAVI, which must be weighed against the anticipated short-term survival advantage and benefits of a less invasive procedure, will be highlighted. Participants will be informed of the intention to use clinical records, GP contact and central NHS databases administered by the Health and Social Care Information Centre and its counterparts in the devolved nations to obtain follow-up data, as required. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish and no less than 24 hours to consider the information and to discuss the study with the Investigator, their GP or other independent parties to decide whether they will participate. Written informed consent will then be obtained by means of a participant dated signature and dated signature of the person who presented the information and obtained consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the site Principal Investigator. The Principal Investigator or a senior clinical Co-Investigator with delegated authority will counter-sign the consent form in cases where the Principal Investigator has not personally

been responsible for obtaining consent. A copy of the signed consent form will be given to the participants. The original signed form will be retained in the study site file and a copy will be filed in the patient's medical notes. The consent form and all other trial documentation at the participating sites will be retained for at least 5 years after the conclusion of the trial.

5.5.2 Screening and eligibility assessment

5.5.2.1 Identification of eligible participants

Participants will be identified by the clinical teams (cardiologists and cardiac surgeons) and study nurses reviewing out-patient referrals and hospital in-patients to identify patients aged ≥70 years, referred for consideration of intervention for severe symptomatic aortic stenosis. Those who have one or more factors that are known to be associated with increased operative risk will be reviewed by a Multi-Disciplinary Team (MDT). In patients aged ≥80 years, no additional risk factors will be required to justify referral for review by the MDT, as advanced age is in itself a significant predictor of operative risk. Data from the UK TAVI registry also suggest that 30-day survival after TAVI, at 93%, is now comparable to that observed after surgical AVR in patients aged over 80 years (94% and 91% in isolated AVR and AVR with CABG respectively). Although long-term outcomes beyond 3 years after TAVI are uncertain, the relatively short life expectancy in this age group (35% and 44% mortality at 5 years after isolated AVR and AVR with CABG respectively) suggests that may be a reasonable trade-off against the short-term advantage of avoiding conventional open-chest surgery and a shorter hospital stay and convalescence.

The clinical teams at each site will be asked to refer for consideration by the MDT, all patients fulfilling the following criteria:

- *Severe symptomatic aortic stenosis, <u>and</u> either:*
- *Age ≥80 years (this will in itself be sufficient to prompt referral), or*
- *Age ≥70 years, with one or more features associated with increased operative risk*

Features associated with increased operative risk include but are not limited to:

- *Frailty or general debility*
- *Chronic pulmonary disease*
- *Previous cardiac surgery or hostile mediastinum*
- *Extracardiac arteriopathy*

- *Neurological dysfunction*
- *Impaired renal function*
- *Impaired left ventricular function*
- *Diabetes mellitus*
- *Pulmonary hypertension*
- *Low BMI*

5.5.2.2 MDT process

The MDT process is recommended in the National Commissioning Framework for TAVI and in the position statement of the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS). It is thus already well established as a part of routine clinical practice in all centres that are currently involved in TAVI. The MDT will typically comprise at least two cardiac surgeons, one or more interventional cardiologists skilled in TAVI, experts in cardiac imaging, a cardiac anaesthetist, a geriatrician and a specialist nurse.

The role of the MDT is to review all of the clinical data in each case and to assess the risk/benefit ratio of conventional AVR and TAVI. The Logistic EuroSCORE and STS score will be used in a discretionary manner, in view of their limited predictive accuracy. It is anticipated that patents recruited will be likely to have an STS score between 4% and 12% (i.e. an intermediate- to high-risk cohort). However, these will not be strict thresholds for inclusion and patients with higher or lower scores may be included if the MDT believes that there is clinical equipoise regarding the choice of intervention.

The precise format of the MDT will be determined at each individual site but the fundamental requirement will be to sequentially address the following questions:

- *Does the patient have severe symptomatic aortic stenosis and would they benefit from intervention to relieve the stenosis?*
- *Is conventional surgical AVR clinically appropriate and technically feasible?*
- *Is the operative risk increased to the extent that, in the current state of knowledge, it is reasonable to consider TAVI as an alternative?*
- *Is TAVI technically feasible (based on anatomical assessment) with locally available technologies?*

- *Is there collective equipoise regarding the relative merits of surgical AVR and TAVI?*

If all of these questions are answered in the affirmative, the patient may be considered eligible for participation in the trial. If anatomical features suggest that a patient would be best treated by a specific TAVI technology that is not available locally, the patient may be offered the option of referral to an alternative study site if they wish to participate in the trial.

It is recognised that the risk threshold at which different surgeons will feel that consideration of TAVI is appropriate in an operable patient will vary, reflecting the experience and judgement of the individual concerned and their interpretation of the available evidence. For this reason, the assessment of eligibility for the trial will be decided locally and will not be bound by an arbitrary EuroSCORE or risk threshold. Thus, although all patients aged ≥80 years will potentially be eligible for the trial, it will be for the local surgical team and the MDT to determine whether consideration of TAVI is appropriate in each individual case. It is likely that the trial population will encompass a fairly wide range of operative risk (STS score between 4% and 12%), which will enable the interaction between baseline risk and treatment effect to be assessed. Data from the UK registry have shown that in patients with a very high EuroSCORE (>40), outcomes are particularly poor. The lessons learned from the registry data are widely used to aid patient selection, with a trend already evident to consider TAVI in patients at lower risk than when the procedure was first introduced. Thus, 76% of patients in the UK TAVI registry had a EuroSCORE of 20 or lower and this is likely to be reflected in the trial.

The proposed approach, whereby an expert MDT determines when there is clinical equipoise regarding the relative merits of two alternative interventions, rather than employing rigid and arbitrary inclusion or exclusion criteria, has been successfully used in previous trials of percutaneous transluminal coronary angioplasty (PTCA) versus CABG such as SoS[28] and SYNTAX.[29]

The outcome of the MDT review and any decisions regarding treatment planning will be recorded in each case. A screening log of all patients recommended for consideration of enrolment by the MDT will be maintained at each site.

Patients who are not suitable for randomisation will be treated as deemed clinically appropriate by the MDT, with surgical AVR, TAVI or conservative therapy. Patients who are eligible for randomisation but decline to participate in the RCT will be offered surgical AVR. TAVI will only be available in this group within the RCT. All patients receiving TAVI (within or outside the trial) will have their data entered in the national UK TAVI Registry, in accordance with usual practice. Similarly, all patients receiving surgical AVR (within or outside the trial) will have their data entered in the SCTS National Adult Cardiac Surgery Database.

5.5.2.3 Concomitant coronary artery disease

Patients with concomitant coronary artery disease (CAD) will also be eligible to participate in the trial, as the majority of this elderly patient group will have at least some degree of coronary artery disease. In the UK TAVI registry, 48% of patients receiving TAVI had at least a 50% stenosis in one or more major epicardial coronary arteries. In the cardiac surgical database, approximately 42% of patients having AVR also had CABG. The MDT will assess and record the extent of any CAD, classifying patients according to whether or not they have greater than 50% stenosis of any major vessel. In those with significant CAD, the MDT will then consider the appropriate treatment strategy. If the patient has CAD for which the MDT considers that only surgical revascularisation would be appropriate, the patient will not be eligible for the trial and will be offered surgery. If the patient has CAD that does not require treatment or could reasonably be treated either by CABG or by PTCA, the patient will be eligible for the trial.

The surgeons in the MDT will be asked to indicate whether, in the event that the patient were treated by surgical AVR, the intention would be to perform concomitant CABG and this will form the basis for stratification at randomisation. The intended target vessels will be identified and recorded. If the patient is randomised to receive TAVI, they will either receive TAVI alone or a hybrid procedure, with PTCA typically being performed about two weeks prior to the TAVI procedure. The decision regarding whether and when PTCA should be performed will rest with the MDT. Whilst this may result in some imbalance in the numbers of patients receiving revascularisation in the two arms of the RCT, this approach reflects clinical practice and is wholly consistent with the pragmatic nature of the trial, which aims to compare a transcatheter (TAVI) strategy with an open-chest surgical strategy. Tracking of re-intervention, quality of life

and mortality during long-term follow-up will disclose any adverse consequence of a decision not to revascularise before the TAVI procedure. Stratification at randomisation, according to intention to revascularise if assigned to surgical AVR, and pre-specified sub-group analyses, according to intended and actual revascularisation, will enable any interaction with the treatment effect to be assessed. It is, however, noteworthy that in the UK TAVI registry, neither the presence of CAD nor its extent (one, two or three-vessel disease) had any significant influence on mortality at one-year.

To summarise, patients with concomitant CAD (≥1 lesion with >50% stenosis in a major epicardial coronary artery) will be dealt with by the MDT in the following manner:

i) MDT decides no intervention required on CAD irrespective of valve treatment → eligible for enrolment in RCT;
ii) MDT decides that the patient could reasonably undergo treatment with AVR +/- CABG, or TAVI +/- PTCA → eligible for enrolment in RCT;
iii) MDT decides that the patient requires CABG (irrespective of valve disease) → not eligible for enrolment in RCT; advise surgical AVR with CABG.

5.5.3 Baseline assessment

Patients entering the RCT will undergo assessment of clinical status and symptoms, using the Canadian Cardiovascular Society (CCS) grading scale for angina[30] and the New York Heart Association (NYHA) classification for breathlessness and heart failure.[31] Functional capacity will be assessed using the Nottingham Extended Activities of Daily Living (NEADL) Scale[32] and a 6-minute walk test.[33] Cognitive function will be assessed using the Mini-Mental State Examination (MMSE).[34] Generic health-related quality of life will be assessed using the EuroQoL EQ-5D-5L (EQ-5D-5L)[35] This is an instrument based on the original EuroQoL EQ-5D (now known as the EQ-5D-3L),[36] which has been developed with the intention to improve sensitivity and reduce ceiling effects.[37] There is no recognised disease-specific quality of life instrument specifically designed or validated for use in aortic stenosis but the Minnesota Living with Heart Failure Questionnaire will be used to assess the impact of breathlessness and heart failure.[38] The patient resource-use questionnaire will also be administered to establish a baseline for use in the economic analysis. Details of the clinical assessment instruments and questionnaires are presented in Appendix C.

An assessment of frailty will be made at baseline to assess its prognostic significance with respect to adverse procedural and post-procedural outcomes. The frailty assessment will comprise the well-validated Fried criteria,[39] which permit stratification between non-frail, pre-frail and frail states, according to the number of criteria that are met. The Fried criteria include hand-grip strength, assessed using a dynamometer, which has been shown independently to predict mortality.[40] Frailty will also be assessed using the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale,[41] which requires the healthcare professional conducting the baseline assessment to judge which of seven categories best describes the status of the participant. Details of the frailty assessment are presented in Appendix D.

A detailed echocardiographic study will be performed at baseline according to the protocol detailed in Appendix E. This will be repeated at the 6-week and one-year follow-up visits. All echocardiographic studies will be recorded on DVD and sent to an experienced central Core Laboratory for independent review. Blood pressure, a 12-lead ECG, haemoglobin and serum creatinine will be recorded.

The procedures and assessments to be performed at the baseline and follow-up visits are summarised in Appendix F.

5.5.4 Randomisation

Eligible participants, who have given written informed consent, will be randomly assigned to receive either TAVI or conventional surgical AVR. Randomisation will be by minimisation, including an 80% probabilistic element[42] using the following factors:

- Age: 70-79 years, ≥80 years
- Centre (hospital)
- Presence or absence of coronary artery disease which is considered to require revascularisation if the patient were treated by surgical AVR

The minimisation will be seeded by randomising the first 30 patients using simple randomisation. Subject numbers will be assigned sequentially as each subject enters the study.

5.6 Follow-up Assessments

Prior to hospital discharge, participants will undergo clinical review. The EQ-5D-5L will be administered over the telephone at 2 weeks, or in hospital if the patient has not yet been discharged.

Participants will attend for follow-up visits at 6 weeks (post-procedure) and 12 months (post-randomisation). At each visit, participants will undergo assessment of clinical status and symptoms, using the CCS scale for angina, and the NYHA class will be assessed. Functional capacity will be assessed using the NEADL Scale and a 6-minute walk test. Cognitive function will be assessed using the MMSE. Quality of life will be assessed using the EQ-5D-5L and the Minnesota Living with Heart Failure Questionnaire. Participants will also undergo echocardiography and the recorded images will be sent to the central Core Laboratory for independent review. Blood pressure, a 12-lead ECG, haemoglobin and serum creatinine will be recorded. The 30-day post-treatment safety assessment will be informed by data collected at the 6 week visit.

Interim follow-up will comprise a telephone assessment at 3 months (post-procedure) and 6 months (post-randomisation) to assess clinical status and symptoms (CCS scale for angina and NYHA class), hospitalisations, major cardiovascular events and vital status. The EQ-5D-5L quality of life questionnaire will be administered at these time points, over the telephone. The clinical information obtained will be supplemented by a telephone call to the General Practitioner, if required. At every follow-up, the current place of residence (e.g. home, supported residential care, nursing home or hospital) of the participant will be recorded.

Long-term annual clinical follow-up will continue for a minimum of 5 years to assess quality of life, need for re-intervention, cardiovascular morbidity and mortality. In many centres, it is no longer common practice to bring patients back to the hospital for annual review. In order to minimise the burden on this elderly patient group, follow-up beyond one year will use brief clinical and resource-use questionnaires and the EQ-5D-5L administered over the telephone unless the patient is attending for routine clinical follow-up. Telephone contact may also be made with the patient's family or carers in the event of failure to respond or a need for additional information. Additional data will be obtained by review of clinical records and contact with the patient's GP, as

required. Long-term mortality and hospitalisation will be tracked using data from the Health and Social Care Information Centre in England and the corresponding agencies in the devolved nations.

5.7 Definition of End of Trial

The end of trial is the date of the last visit or telephone follow-up of the last participant.

5.8 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In the event that a participant wishes to withdraw from attendance at follow-up visits, they will be invited to continue with telephone follow-up. If they decline further contact with the study team, permission will be sought to continue passive follow-up, with periodic review of hospital records and contact with the participant's General Practitioner. Vital status will be tracked through the NHS Information Centre, in any event. The reason for withdrawal will be recorded in the Case Report Form (CRF). If a participant loses capacity during the trial they will be withdrawn from further active participation. Hospitalisation and mortality data will continue to be collected from the Health and Social Care Information Centre in England and the corresponding agencies in the devolved nations, subject to the required regulatory approvals.

5.9 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital and general practice records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical charts, laboratory and pharmacy records, diaries, imaging data and reports, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

6 TREATMENT OF TRIAL PARTICIPANTS

6.1 Description of Study Treatment

TAVI is a procedure whereby a prosthetic aortic valve is delivered into the heart via a catheter that is introduced to the arterial system by puncture of the femoral artery in the

groin, the subclavian artery at the top of the arm or the ascending aorta via a mini-thoracotomy and advanced to the heart, retrogradely crossing the aortic valve. An alternative to this trans-arterial approach is the trans-apical approach, which is most often used in patients with diseased or narrow peripheral arteries. With this technique, the valve is introduced directly through the chest wall by a mini-thoracotomy, entering the heart through the apex of the left ventricle before being passed antegradely across the aortic valve. The prosthetic valve is implanted within the native diseased valve, which is pushed aside in the implantation procedure.

The study permits the use of any CE-marked TAVI device, subject to satisfactory and sufficient global and local user experience, as adjudicated by the Trial Steering Committee. There are currently three CE-marked devices in widespread clinical use in Europe, the Medtronic CoreValve™ self-expanding bioprosthesis and the Edwards Sapien™ and Sapien XT™ balloon-expandable bioprostheses. All of these are approved for use in the trial in their current form and with the inclusion of any minor design improvements that may be made in the future.

Surgical AVR is a well-established procedure. It is performed with the patient on cardiopulmonary bypass with cardioplegic cardiac arrest. Access is usually via a median sternotomy but can be via a mini/upper hemi-sternotomy or a right anterior thoracotomy. It will involve excision of the native valve and replacement of the valve by suturing a new prosthetic valve into place. Any commercially available stented or stentless valve may be used. The newer sutureless valves cannot be implanted in this trial, as they represent another novel technology in their own right. The trial is not designed or powered to be able to evaluate comparative clinical outcomes with this type of valve. The precise location and nature of any concomitant coronary artery bypass grafts that are to be placed will be pre-specified at the MDT meeting but will ultimately be at the discretion of the operator at the time of the surgical procedure.

Treatment with TAVI and surgical AVR will be in accordance with the site's Standard Operating Procedures or Clinical Guidelines, using whatever technique, access route and valve type are deemed clinically appropriate.

6.2 Concomitant Treatment

Throughout the study Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

6.3 Post-trial Treatment

Participants will continue under normal clinical care.

7 SAFETY REPORTING

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational device or the comparator.

NOTE 2: This includes events related to the procedures involved (any procedure in the protocol).

NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

7.1.2 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device. This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the device. It also includes any event that is the result of a user error or intentional misuse.

7.1.3 Device deficiency

An inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

7.1.4 Investigational medical device

A medical device being assessed for safety or performance in a clinical investigation.

NOTE: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

7.1.5 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death,

- Is life-threatening, *NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. *NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.*

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

7.1.6 Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.7 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the protocol or in the product information relating to the device.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the protocol, patient information sheet or product information relating to the device.

7.1.8 Causality

The relationship of each adverse event to the trial intervention must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from administration of the trial intervention. It cannot reasonably be attributed to any other cause.

Not related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

7.2 Expected Adverse Events and Adverse Device Effects

Some adverse events and adverse device effects occurring during the trial will be expected, as a consequence of the underlying condition, diagnostic tests or investigational procedures, and the recognised complications of TAVI and surgical AVR. These include but are not limited to:

- Death
- Stroke or transient ischaemic attack
- Myocardial infarction
- Need for elective or emergency surgery or re-intervention
- Need for haemodynamic support
- Vascular complications
- Prosthetic valve dysfunction
- Paravalvular regurgitation
- Valve migration or embolisation
- Cardiac perforation
- Cardiac tamponade
- Annular rupture
- Bleeding
- Bruising or haematoma at vascular access site
- Wound, systemic or respiratory infection
- Pleural effusion
- Mediastinitis
- Endocarditis
- Renal failure
- Liver failure
- Respiratory failure
- Conduction disturbance
- Need for permanent pacemaker implantation
- Cardiac arrest

- Cardiac arrhythmia
- Allergic reaction to contrast media
- Adverse reaction to anaesthesia
- Wound dehiscence
- Gastro-intestinal complications
- Thrombo-embolic complications

7.3 Safety Reporting Procedures

7.3.1 Reporting of Adverse Events (AEs) and Adverse Device Effects (ADEs)

All AEs and ADEs observed by the investigator or reported by the participant, whether expected or unexpected and serious or non-serious, will be recorded on the CRF, which should be submitted to the trial coordinating centre at the earliest opportunity. This includes all events from the first trial-related activity after the participant has signed the consent form until the end of the trial, as defined in section 5.7 of the protocol.

The following do not need to be recorded as adverse events, if they are recorded as medical history on the CRF at the start of the trial:

- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity;
- Pre-existing conditions found as a result of screening procedures.

For all AEs and ADEs, the information recorded will include a description of the event, date of onset, end-date, assessment of severity, seriousness and relatedness to the study treatment (as judged by a medically qualified investigator), assessment of expectedness, details of any other suspect drug or device, and details of any action taken. All AEs and ADEs will be followed until resolution or until the event is considered stable and outcome data will be submitted to the trial coordinating centre when available.

The local Principal Investigator will be responsible for the initial assessment of seriousness, causality and expectedness of AEs and ADEs. In assessing causality, events will be categorised as ‘definitely related’, ‘probably related’, ‘possibly related’, ‘unlikely to be related’ or ‘not related’ to the study treatment. Events with ’definite’, ‘probable’ or ‘possible’ relatedness will be classified as related. If the Chief Investigator

or Sponsor disagrees with the local Principal Investigator's assessment, they may seek further clarification but will not downgrade the Principal Investigator's assessment of relatedness other than by agreement.

In view of the known safety profile of TAVI and surgical AVR and the unblinded nature of the study, expected AEs and ADEs, as specified in section 7.2, whether serious or not, are not considered to require additional safety reporting, other than by way of the CRF.

Data on all adverse events collected during the course of the trial will regularly be reported to the Data Monitoring Committee for review.

7.3.2 Reporting of Unexpected Serious Adverse Device Effects (USADEs)

AE and ADE that are considered to be serious, unexpected and causally related to the study treatment or research procedures will be notified to the trial coordinating centre immediately, using the appropriate form for an urgent safety report. Upon receipt by the trial coordinating centre, the event details will immediately be passed to the Sponsor and to the Chief Investigator or a designated colleague, who will review the event. The Sponsor will submit a report of any related and unexpected SAE, and any USADE to the main REC within 15 days of their becoming aware of the event. The R&D Department of the local host NHS organisation will also be informed by the local Principal Investigator, if applicable, according to local Standard Operating Procedures (SOP) and policies, immediately they become aware of the event.

7.3.3 Reporting of device deficiencies

In the event of a device deficiency or an adverse incident involving a device or its instructions for use (including user/device interface problems), the local Principal Investigator should consider informing the device manufacturer and the Medicines and Healthcare products Regulatory Agency (MHRA) Adverse Incident Centre, in accordance with the Devices Vigilance System requirements and standard clinical practice.

Adverse events will not otherwise be reported to the MHRA, as this is a trial of CE-marked devices being used for their intended purpose and is consequently not subject to regulation by the Competent Authority in accordance with the Medical Devices Regulations 2002.

7.4 Annual Safety Report

The Chief Investigator will include a report on the safety of participants in the annual progress report to the main REC.

8 STATISTICS

8.1 Sample Size

The sample size calculation is based on the assumptions of one-year mortality of 15% for surgical AVR and no real difference in one-year mortality between TAVI and surgical AVR. The non-inferiority margin has been set at an absolute difference of 7.5% in one-year mortality favouring surgical AVR. The number of subjects required to ensure, with 90% power, that the upper limit of the one-sided 95% confidence interval for the treatment difference is not above the non-inferiority margin is 395 per treatment group, calculated using nQuery Advisor software. Allowing for a 2% dropout rate in both arms, a sample of at least 808 patients is required.

If a one-sided 2.5% significance level (equivalent to a two-sided 5% significance level) is used, then the sample size of 808 patients will give 84.7% power with the same parameters. If one-year mortality following surgical AVR is 20% instead of 15%, the sample size of 808 patients would have 84.6% power to demonstrate non-inferiority using the same parameters and a one-sided 5% significance level.

The PARTNER A trial demonstrated a 2% difference in all-cause mortality in favour of TAVI over surgical AVR, although the eligibility criteria were somewhat different from those for the UK TAVI trial. If this translates to a 1% difference in favour of TAVI, then fewer patients would be required. The sample size assumptions will be monitored by the independent Data Monitoring Committee as the trial progresses and they will advise the Trial Steering Committee if any adjustment to the sample size is deemed necessary.

8.2 Statistical Analysis

A separate Statistical Analysis Plan (SAP) will contain full details of all statistical analyses and will be prepared early in the trial and finalised before the primary analysis database lock.

The primary statistical analysis will use an intention-to-treat approach, with all patients analysed as randomised. All-cause mortality at one year will be analysed using logistic regression modelling in a multivariate framework, adjusting for stratification factors. Centre by treatment interactions will be examined and if significant, results will be presented by centre. Statistical tests will be 2-sided at the 5% level of significance (equivalent to 1-sided 2.5% significance level). A figure showing the one-sided 95% confidence interval and the non-inferiority margin for the overall treatment effect will be presented. Other important covariates will be considered for inclusion in the model, including age, pre-operative risk score, frailty, left ventricular function, concurrent or proximate coronary artery revascularisation and pre-specified comorbidities. Sub-group analyses will be undertaken for a number of pre-specified sub-groups (including age, pre-operative risk score, frailty, left ventricular function, concurrent or proximate coronary artery revascularisation, pre-specified intention to revascularise if assigned to receive surgical AVR, and pre-specified comorbidities) using appropriate regression models (as above) with terms included for treatment by covariate (defining the sub-groups) interactions.

All event-related outcomes (including mortality, stroke, and length of hospital stay) will be analysed using survival analysis techniques to allow for censoring and differential follow-up, including Kaplan-Meier plots and Cox proportional hazards regression in a multivariate framework to adjust for stratification factors and other potential confounders. Categorical and ordinal outcomes (for example symptoms, functional capacity, cognitive function and complications) will be analysed using Chi-squared tests and logistic (ordinal) regression to allow for stratification factors and potential confounders. Continuous outcomes (for example, quality of life and echocardiographic parameters) will be analysed using parametric or non-parametric tests, as appropriate.

A cost-effectiveness analysis will be undertaken using quality-adjusted survival methods to allow for mortality and censoring.

The distribution of missing data will be explored to assess the assumption of data being missing at random. Multiple-imputation will be utilised, if appropriate and full details will be provided in the SAP.

A sensitivity analysis will assess the internal validity of the trial results by performing a per-protocol analysis on all subjects who adhere to the major criteria in the protocol, as

determined by a blinded analysis immediately prior to the primary outcome database lock.

A safety analysis will include all patients who received the actual treatment under consideration.

Subject to regulatory approval, external validity will be assessed by comparing outcomes from the randomised study population with anonymised outcome data from the SCTS National Adult Cardiac Surgery Database and the national UK TAVI Registry for patients who meet the eligibility criteria but do not proceed to randomisation.[44]

9 DIRECT ACCESS TO SOURCE DATA/ DOCUMENTS

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

10 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, the principles of ICH GCP, the Research Governance Framework, other relevant regulations and standard operating procedures.

Regular monitoring will be performed, as determined by the Sponsor, in line with the principles of ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

SITU will have responsibility for the day-to-day management of the trial, in collaboration with the Chief Investigator and the Trial Management Group.

A Trial Steering Committee (TSC) will be appointed to provide overall supervision for the trial on behalf of the Sponsor and the Funder, and to ensure that the trial is conducted in accordance with GCP. Membership of the TSC will include an independent Chair, at least two other independent members and a lay representative.

A separate TSC charter will contain full details of the Committee and its roles and reporting structure.

An independent Data Monitoring Committee (DMC) will be established to safeguard the interests of trial participants, potential participants and future patients, to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DMC will make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The DMC will consider what interim analyses are necessary, review the data from any such analyses and advise the TSC of any implications for the design or conduct of the trial. The TSC will make any decisions about continuation or otherwise of the trial. A separate DMC charter will contain full details of the Committee and its roles and reporting structure.

11 SERIOUS BREACHES

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial”.
In the event that a serious breach is suspected, the Sponsor will be informed as soon as possible and within 7 days of the investigator becoming aware of the event.

12 ETHICS

12.1 Declaration of Helsinki

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

12.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that the study is conducted in full conformity with relevant regulations and with the principles of the ICH Guidelines for Good Clinical Practice.

12.3 Approvals

The protocol, consent form and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC) and to the host institution(s) for written approval. The Chief Investigator will submit and, where necessary, obtain approval

from the above parties for all substantial amendments to the original approved documents.

12.4 Participant Confidentiality

All personal and medical information obtained from participants during the study will be treated in strict confidence and no data will be disclosed to third parties, except as specifically stated in the protocol and in the patient information sheet or consent form. With the exception of the initial recording and transfer of the personal data that are required to identify study participants to the Health and Social Care Information Centre, all study data that are recorded at the participating sites and transmitted to the coordinating centre will be pseudonymised. Participants will be identified only by their initials, month and year of birth, and a participant ID number on the CRF and in the main study database. Full postcodes will not be included in the main study database but they will be cross-referenced to derive deprivation indices and geographical distances from the treatment centre, for use in the health economic analysis. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13 DATA HANDLING AND RECORD KEEPING

All study data will be entered by the study team at participating sites using an electronic CRF and uploaded to the study database by a web-based Remote Data Capture system. The study database will be hosted on a secure central server. The system will be fully validated and compliant with the requirements of ICH GCP. Paper records and all source data will be retained at the participating site for at least 5 years after the conclusion of the trial. Central trial records will be retained by the Sponsor for at least 15 years after the conclusion of the trial.

14 FINANCE AND INSURANCE

14.1 Compensation for Harm

Negligent Harm: Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Leicester. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

Non-Negligent Harm: There will be no indemnity or compensation for non-negligent harm occurring as a consequence of participation in the trial.

15 PUBLICATION POLICY

The investigators are committed to the publication and widespread dissemination of the results of the trial. The recommendations of any interested party concerning content shall be taken into consideration in the final preparation of presentations and manuscripts for publication but the final decision shall rest with the Trial Management Group. All proposed publications and presentations resulting from or relating to the study must be submitted to the Trial Management Group for review and approval prior to submission for publication or presentation.

Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged. It is intended that the Principal Investigators from the highest-recruiting centres will be invited to participate fully in the preparation and authorship of the main manuscripts resulting from the trial.

The funder will be acknowledged in all publications arising from the trial.

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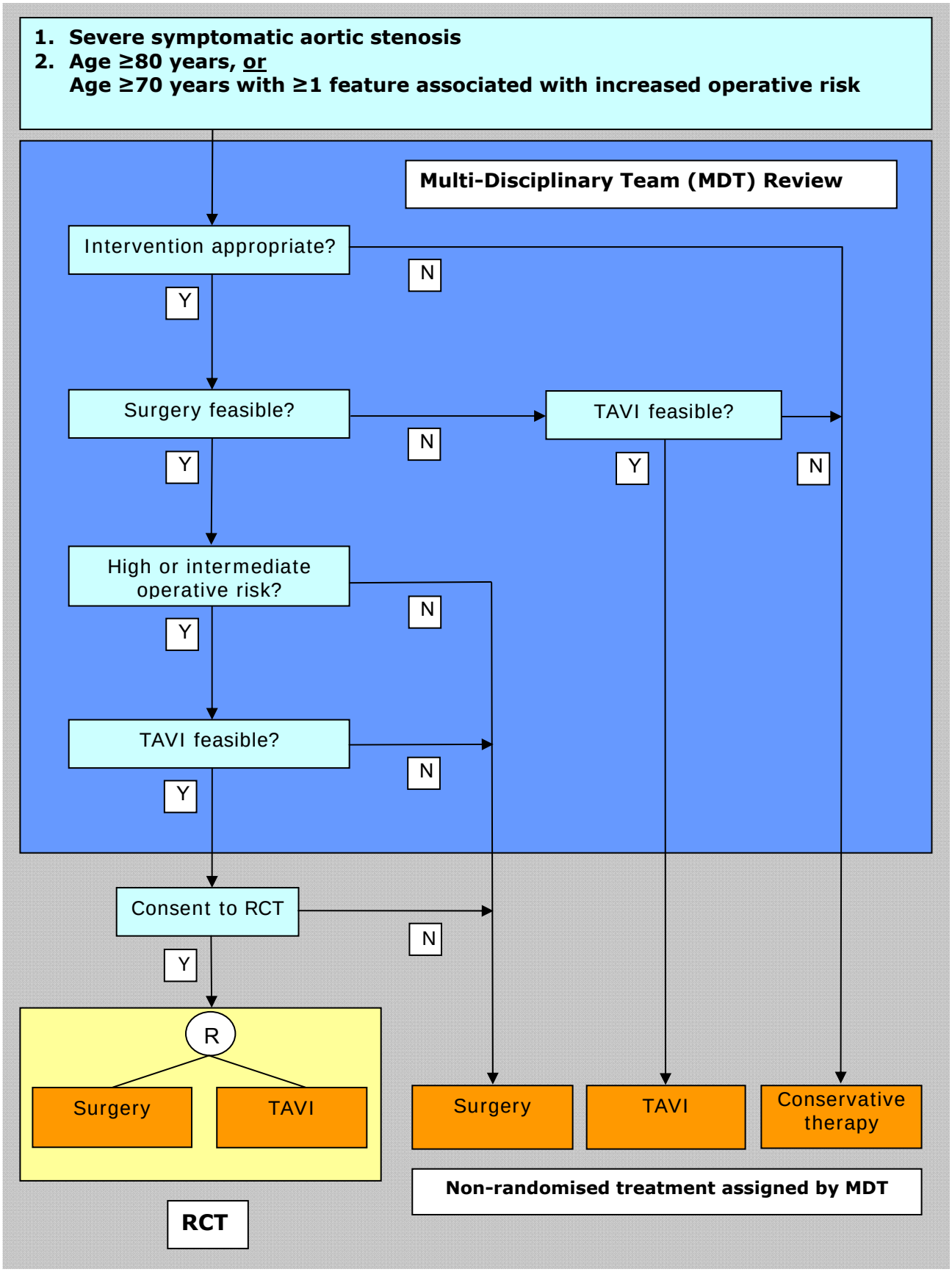
17 APPENDIX A: STUDY FLOW CHART



18 APPENDIX B: OUTCOME DEFINITIONS

18.1 All-cause mortality

Death from any cause at any time after randomisation (for the primary analysis based on intention-to-treat)

18.2 Cardiovascular mortality

Cardiovascular mortality

Any of the following criteria:

- Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)
- Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events
- Sudden or unwitnessed death
- Death of unknown cause

Non-cardiovascular mortality

Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

18.3 Procedural success

- Absence of procedural mortality AND
- Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
- Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation)

18.4 Stroke and Transient Ischaemic Attack (TIA)

Diagnostic criteria:

- Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Stroke: Duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
- TIA: Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct.
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist
- Confirmation of the diagnosis by at least one of the following:
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification:

- Ischaemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
- A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischaemic or haemorrhagic

Stroke definitions:

- Disabling stroke: a modified Rankin scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline;
- Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

The degree of disability or dependence after a stroke will be assessed by an appropriately trained assessor, using the Modified Rankin Scale (mRS).[45]

Modified Rankin Scale:

Score	Criteria
0	No symptoms.
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

18.5 Vascular complications

Major vascular complications:

- Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, compartment syndrome,
- percutaneous closure device failure) leading to death, life-threatening or major bleedinga, visceral ischaemia, or neurological impairment OR
- Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
- The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment OR
- Any new ipsilateral lower extremity ischaemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- Surgery for access site-related nerve injury OR
- Permanent access site-related nerve injury

Minor vascular complications:

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, haematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischaemia, or neurological impairment OR
- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

Percutaneous closure device failure:

- Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

18.6 Bleeding

Life-threatening or disabling bleeding

- Fatal bleeding (BARC[a] type 5) OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
- Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
- Overt source of bleeding with drop in haemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units (BARC type 3b)

Major bleeding (BARC type 3a)

- Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND
- Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding (BARC type 2 or 3a, depending on the severity)
Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling, or major

[a]BARC: Bleeding Academic Research Consortium[46]

18.7 Infective endocarditis

Any one of the following:

- Fulfilment of the Duke endocarditis criteria
- Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation
- Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy

18.8 Other complications

Conversion to open surgery:
Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications

Unplanned use of cardiopulmonary bypass (CPB):
Unplanned use of CPB for haemodynamic support at any time during the TAVI procedure

Coronary obstruction:
Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure

Ventricular septal perforation:
Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure

Mitral valve apparatus damage or dysfunction:
Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure

Cardiac tamponade:

Evidence of a new pericardial effusion associated with haemodynamic instability and clearly related to the TAVI procedure

Valve thrombosis:

Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis

Valve malpositioning:

- Valve migration

After initial correct positioning, the valve prosthesis moves upwards or downwards, within the aortic annulus from its initial position, with or without consequences

- Valve embolization

The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus

- Ectopic valve deployment

Permanent deployment of the valve prosthesis in a location other than the aortic root

TAV-in-TAV deployment:

An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure

18.9 Myocardial infarction

Peri-procedural MI (≤72 h after the index procedure):

- New ischaemic symptoms (e.g. chest pain or shortness of breath), or new ischaemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, haemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
- Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB. If cardiac biomarkers are increased

at baseline (>99th percentile), a further increase in at least 50% post-procedure is required AND the peak value must exceed the previously stated limit

Spontaneous MI (>72 h after the index procedure):

Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with the evidence of myocardial ischaemia with at least one of the following:
    - Symptoms of ischaemia
    - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)]
- New pathological Q-waves in at least two contiguous leads
- Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Pathological findings of an acute myocardial infarction

18.10 Conduction disturbance and arrhythmia

Data elements to be collected include:

- Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and the presence of permanent pacemaker[a]
- Implant-related new or worsened cardiac conduction disturbance (new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), third-degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring a permanent pacemaker implant
- Persistent or transient high-degree AV block. High-grade AV block is persistent if it is present every time the underlying rhythm is checked
- New permanent pacemaker implantation, with precision of the indication and the number of days post-implant of the placement of new permanent pacemaker
- New-onset atrial fibrillation (or flutter)[b]

- Any new arrhythmia resulting in haemodynamic instability or requiring therapy[c]

[a]Type of permanent pacemaker should be recorded (e.g. defibrillator, single *vs* dual chamber, biventricular).
[b]New-onset atrial fibrillation (or flutter) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 s on a rhythm strip.
[c]Therapy includes electrical/medical cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate controlling therapy).

18.11 Renal replacement therapy (RRT)

Acute RRT:
Haemofiltration, haemodialysis or peritoneal dialysis occurring during the inpatient episode
Chronic RRT:
Establishment of new chronic renal dialysis

Acute kidney injury within seven days of the index procedure will be classified according to the AKIN classification:[47]

Stage 1:
Increase in serum creatinine to 150-190% (1.5-1.99 x increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/l) OR
Urine output <0.5 mL/kg/h for >6 but <12 h
Stage 2:
Increase in serum creatinine to 200-299% (2.0-2.99 x increase compared with baseline) OR Urine output <0.5 mL/kg/h for >12 but <24 h
Stage 3:[a]
Increase in serum creatinine to ≥300% (>3 x increase compared with baseline) OR serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) OR
Urine output <0.3 mL/kg/h for ≥24 h OR
Anuria for ≥ 12 h

[a]Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria

18.12 Re-intervention:

Repeat percutaneous or surgical invasive procedure to modify function or performance of the aortic valve complex (excluding return to theatre for bleeding)

19 APPENDIX C: CLINICAL ASSESSMENT INSTRUMENTS

19.1 Canadian Cardiovascular Society grading scale for angina

Class	Description
I	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina results from strenuous or rapid or prolonged exercise at work or recreation.
II	Slight limitation of ordinary activity: walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, in cold wind, or when under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and under normal conditions.
II	Marked limitations of ordinary physical activity: walking one or two blocks on the level and climbing more than one flight under normal conditions.
IV	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.

19.2 New York Heart Association Classification for Breathlessness and Heart Failure

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
II	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

19.3 Nottingham Extended Activities of Daily Living

Nottingham Extended ADL Scale

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the last few weeks.

DID YOU.....	Not at all	with help	on your own	on your own with difficulty
1. Walk around outside?	☐	☐	☐	☐
2. Climb stairs?	☐	☐	☐	☐
3. Get in and out of a car?	☐	☐	☐	☐
4. Walk over uneven ground?	☐	☐	☐	☐
5. Cross roads?	☐	☐	☐	☐
6. Travel on public transport?	☐	☐	☐	☐
7. Manage to feed yourself?	☐	☐	☐	☐
8. Manage to make yourself a hot drink?	☐	☐	☐	☐
9. Take hot drinks from one room to another?	☐	☐	☐	☐
10. Do the washing up?	☐	☐	☐	☐
11. Make yourself a hot snack?	☐	☐	☐	☐

	No	With help	On your own with difficulty	On your own
12. Manage your own money when out?	☐	☐	☐	☐
13. Wash small items of clothing?	☐	☐	☐	☐
14. Do your own housework?	☐	☐	☐	☐
15. Do your own shopping?	☐	☐	☐	☐
16. Do a full clothes wash?	☐	☐	☐	☐
17. Read newspapers or books?	☐	☐	☐	☐
18. Use the telephone?	☐	☐	☐	☐
19. Write letters?	☐	☐	☐	☐
20. Go out socially?	☐	☐	☐	☐
21. Manage your own garden?	☐	☐	☐	☐
22. Drive a car?	☐	☐	☐	☐

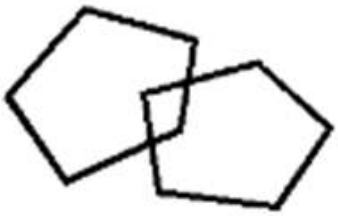
19.4 Mini-Mental State Examination

Folstein Mini Mental State Date _____
Clinic # _____
Name _____ Age ____ Sex ____

___/ 5 What is the: (year) (season) (date) (day) (month) ?
___/ 5 Where are we: (state) (county) (town) (building) (floor) ?
___/ 3 Learn: "apple, table, penny." ____ # of trials.
___/ 5 Subtract serial 7's: (100, 93, 86, 79, 72); or, spell "WORLD" backwards.
___/ 3 Recall: "apple, table, penny."
___/ 2 Name: "pencil" and "watch."
___/ 1 Repeat: "No ifs, ands or buts."
___/ 3 "Take this paper in your right hand, fold it in half, and put it on the floor."
___/ 1 Read and obey: "Close your eyes."
___/ 1 Write a sentence on the back of this card.
___/ 1 Copy the design on the back of this card.

___/ 30 Total (abnormal if < 24; if < 8th grade, then < 21 is considered abnormal.)

Close your eyes.



19.5 EuroQol EQ-5D-5L Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

Self-Care

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

Pain/Discomfort

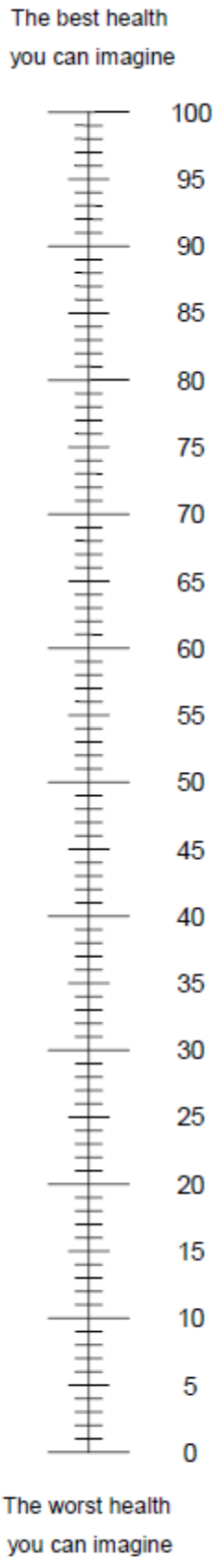
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



19.6 Minnesota Living With Heart Failure® Questionnaire

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**			**Very Little**					**Very Much**
1. causing swelling in your ankles or legs?	0			1	2	3	4	5	
2. making you sit or lie down to rest during the day?	0			1	2	3	4	5	
3. making your walking about or climbing stairs difficult?	0			1	2	3	4	5	
4. making your working around the house or yard difficult?	0			1	2	3	4	5	
5. making your going places away from home difficult?	0			1	2	3	4	5	
6. making your sleeping well at night difficult?	0			1	2	3	4	5	
7. making your relating to or doing things with your friends or family difficult?	0			1	2	3	4	5	
8. making your working to earn a living difficult?	0			1	2	3	4	5	
9. making your recreational pastimes, sports or hobbies difficult?	0			1	2	3	4	5	
10. making your sexual activities difficult?	0			1	2	3	4	5	
11. making you eat less of the foods you like?	0			1	2	3	4	5	
12. making you short of breath?	0			1	2	3	4	5	
13. making you tired, fatigued, or low on energy?	0			1	2	3	4	5	
14. making you stay in a hospital?	0			1	2	3	4	5	
15. costing you money for medical care?	0			1	2	3	4	5	
16. giving you side effects from treatments?	0			1	2	3	4	5	
17. making you feel you are a burden to your family or friends?	0			1	2	3	4	5	
18. making you feel a loss of self-control in your life?	0			1	2	3	4	5	
19. making you worry?	0			1	2	3	4	5	
20. making it difficult for you to concentrate or remember things?	0			1	2	3	4	5	
21. making you feel depressed?	0			1	2	3	4	5	

11/10/04

19.7 Patient resource-use questionnaire

Health Service Use and Carer Information

We would like to know how much contact you have had with the health service over the last 12 months. If you are not exactly sure, we would rather have your best guess than no information at all. Please answer every question, even if the answer is "0".

Over the last 12 months, approximately how many times have you for any reason:

Example: "Been seen by your GP?"	15
1. Been seen by your GP?	
2. Been seen by a practice nurse?	
3. Been seen by a physio or occupational therapist?	
4. Consulted your GP or practice nurse by telephone?	
5. Visited a hospital out-patient clinic?	
6. Been admitted to hospital as a day-case?	
7. Visited a cardiac rehabilitation centre?	
8 Been admitted to hospital overnight?	
8a. If you were admitted to hospital on one or more occasions, for how many nights were you there in total?	

9. Who do you receive help from and how frequently?

Please circle ONE response in each category:

a. Spouse	Daily	Weekly	Monthly or less often	None
b. Other family member	Daily	Weekly	Monthly or less often	None
c. Friend/ neighbour/ volunteer services	Daily	Weekly	Monthly or less often	None
d. Outside help - paid by you	Daily	Weekly	Monthly or less often	None
e. Outside help - provided by Social Services e.g. '*meals on wheels*' or '*home help*'	Daily	Weekly	Monthly or less often	None

Thank you very much for your help

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20 APPENDIX D: FRAILTY ASSESSMENT

20.1 Fried Criteria

The most commonly used international definition of frailty is from Fried *et al*[40] (Cardiovascular Health Study frailty rating scale) and involves assessment of the following:

- Sarcopaenia - defined as the lowest quintile for hand-grip strength, adjusted for body mass index (BMI) and stratified by sex, measured using a standard dynamometer.
- Exhaustion - defined as response of 'a moderate amount of time' or 'most of the time' to either of two statements on the Centre for Epidemiological Studies Depression Scale ('I felt that everything I did was an effort;' 'I could not get going').
- Nutrient–energy imbalance - defined as self-reported unintentional weight loss of 5kg or greater in the previous year.
- Slowness - defined as the slowest quintile for the time required to walk 2.4 meters (8 feet), adjusted for height and stratified by sex – needs timed 2.4 metre walk
- Low physical activity - defined as the lowest quintile for energy expended per week in leisure-time physical activities, stratified by sex, by using the modified Minnesota Leisure Time Activities questionnaire.

The scale treats frailty as a three-level categorical variable: 'not frail' (not meeting any frailty criteria), 'pre-frail' (meeting one or two criteria), and 'frail' (meeting three or more criteria).

Assessment will follow the method used in the Frailty Intervention Trial.[48] The following criteria will be evaluated:

a) Unintentional weight loss:

The participant will be asked whether they have lost more than 4.5 kg unintentionally in the past year and their weight will be measured with scales. This criterion is positive if there is unintentional weight loss of more than 4.5 kg, or greater than 5% of body weight in the previous year.

b) Self-reported exhaustion:

The participant will be read two statements from the Center for Epidemiologic Studies-Depression Scale:

- "I felt that everything I did was an effort"
- "I could not get going"

The participant will then be asked how often in the last week he/she felt this way. 0 = rarely or none of the time, 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), 3 = most of the time. A score of 2 or 3 is a positive response.

c) Weakness:

Grip strength in the dominant hand will be measured using a standard hand-held dynamometer. The best of three attempts will be used. Using a simplification of the cut-off value for grip strength used by Fried *et al*, male participants who score 30 kg or less will be classified as having weak grip strength. Female participants with a score of 18 kg or less will be classified as having weak grip strength.

d) Slow walking speed:

The time to walk four metres will be measured, with or without a walking aid. Those participants with a walking time of six seconds or more will be classified as having slow walking speed. The values used by Fried *et al* have been modified slightly for ease of assessment. Cesari and colleagues[49] determined that older persons with a usual walking speed of one metre per second or less is indicative of poor health outcomes.

e) Low physical activity level:

Participants will meet the criterion for physical inactivity if, in the past three months, they did not perform weight-bearing physical activity, spent more than four hours per day sitting, and went for a short walk once per month or less. This is a modification of the definition used by Cesari and colleagues.[50]

20.2 The Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale

The CSHA Clinical Frailty Scale

1 **Very fit** – Robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

2 **Well** – Without active disease, but less fit than people in category 1

3 **Well, with treated comorbid disease** – Disease symptoms are well controlled compared with those in category 4

4 **Apparently vulnerable** – Although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms

5 **Mildly frail** – With limited dependence on others for instrumental activities of daily living

6 **Moderately frail** – Help is needed with both instrumental and non-instrumental activities of daily living

7 **Severely frail** – Completely dependent on others for the activities of daily living, or terminally ill

IADL

Activities required to live in the community

- Meal preparation
- Ordinary housework
- Managing finances
- Managing medications
- Phone use
- Shopping
- Transportation

ADL

Non-instrumental activities of daily living; related to personal care

- Mobility in bed
- Transfers
- Locomotion inside and outside the home
- Dressing upper and lower body
- Eating
- Toilet use
- Personal hygiene
- Bathing

21 APPENDIX E: ECHOCARDIOGRAPHY PROTOCOL

All centres participating in the trial will be required to submit echocardiographic data and images according to a pre-specified protocol. Those with the facilities and capability to do so will be encouraged also to submit 3-D echocardiographic images. A lead echocardiographer will be identified at each centre to ensure adherence to the protocol and the quality of scanning. Scans will be performed preoperatively, and at the 6-week and 12-month follow-up visits.

Echocardiography protocol

- Blood pressure, height and weight will be required at each time point.

- Parasternal long axis and 2-D guided M mode for left ventricular (LV) dimensions and wall thickness;
  Left ventricular outflow tract (LVOT) diameter (zoomed);
  Aortic annulus diameter (zoomed);
  Colour flow Doppler (CFD) for AR and MR (vena contracta).

- Parasternal short axis LV base and papillary level;
  Aortic valve for morphology;
  Tricuspid for tricuspid regurgitation (TR).

- Right ventricular (RV) inflow view for TR.

- Apical four-chamber for LV volume/ ejection fraction (EF), left atrial (LA) volume/ 3-D dataset;
  Assessment of MR (proximal isovelocity surface area (PISA), if possible);
  Transmitral Doppler, pulsed wave (PW) for forward flow, continuous wave (CW) for regurgitation;
  Tissue Doppler septal and lateral mitral annulus;
  Tricuspid annular plane systolic excursion (TAPSE).

- Apical five-chamber for transaortic gradient - CW, LVOT PW, CFD for AR.

- Apical two-chamber for LV volume/ EF.

- Right parasternal (RPS) and suprasternal (SS) for transvalvar gradient - stand-alone.

- Sub-costal (SC) for inferior vena cava (IVC) diameter and collapse.

Analyses - Comparative Changes following TAVI *vs* AVR

- LV dimensions and volumes (Simpson's);
  3-D volumes;
  LV mass (Devereaux);
  Stress-corrected mid-wall shortening, stress-corrected fractional shortening (FS);
  Tissue Doppler (E/E'), E',Sm, for filling pressure and long axis function;
  2- and 3-D speckle tracking.

- LA volume.

- RV function – TAPSE.

- Peak gradient, mean gradient, valve area, valve area index;
  Qualitative AR, MR,TR, quantitation where possible;
  ZVa (ventriculo arterial impedance).

- Pulmonary artery (PA) pressure.

- Patient-prosthesis mismatch (AVR *vs* TAVI).

Core Laboratory Funct*io*n

All studies will be sent to the Core Laboratory in Dicom compatible digital format on CD. Discs will be marked with the patient's trial number and date of scan but otherwise be anonymised. Core Laboratory analysis will be split between the North West Heart Centre, University Hospitals of South Manchester (UHSM), and King's College Hospital, under the joint Directorship of Professors Simon Ray and Mark Monaghan. 3-D analysis will be performed at King's and other analyses at UHSM. A standard measurement and analysis protocol will be followed at both centres. A proportion of studies will be analysed at both centres to ensure reproducibility of measurements.

22 APPENDIX F: SCHEDULE OF PROCEDURES

Procedures	Visits						
	Baseline	Pre-discharge	6 weeks	3 months *	6 months *	1 year	Years 2 – 5 *
Informed consent	✓						
Demographics	✓						
Medical history	✓						
Concomitant medications	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓			✓	(✓)†
ECG	✓		✓			✓	
Laboratory tests	✓		✓			✓	
Echocardiogram	✓		✓			✓	(✓)†
Coronary angiography	✓						
Eligibility assessment	✓▲						
Randomisation	✓						
Frailty assessment	✓						
Risk assessment and scoring	✓						
Quality of life assessment	✓	(✓)‡	✓	✓	✓	✓	✓
NYHA class/ CCS grade	✓		✓	✓	✓	✓	✓
Functional capacity	✓		✓			✓	
6-minute walk test	✓		✓			✓	
Cognitive function (MMSE)	✓		✓			✓	
Resource-use questionnaire	✓					✓	✓
TAVI or AVR		✓^					
Adverse events	✓	✓	✓	✓	✓	✓	✓

* telephone follow-up

† only if performed in the context of routine clinical follow-up

▲ Eligibility assessment and randomisation should be on the same day

‡ EQ-5D-5L performed at 2 weeks by telephone or in hospital if not yet discharged

^ TAVI or AVR should be performed within 6 weeks from randomisation

23 AMENDMENT HISTORY

Amendment number	Protocol version	Date issued	Author(s) of changes
01	v2.0	31th Jan 2014	Chief Investigator

Section	Page	Amendment
-	3	Inclusion of section for authorisation of final protocol and amendments by Chief Investigator and Sponsor representative.
5.2.3 5.6	21 30	Addition of the use of the patient resource-use questionnaire at baseline and annually beyond the first year.
5.5.1	23	Inclusion of option for Principal Investigator to delegate countersignature of the patient consent form to a senior clinical Co-Investigator, in the event that the Principal Investigator has not personally obtained consent.
5.5.3	28	Removal of Katz index from activities of daily living assessment at baseline.
5.5.3 5.6	28 30	Removal of Medical Outcomes Survey Short Form 12 v2 (SF-12) quality of life questionnaire from baseline and follow-up assessments.
5.5.3 5.6	28 30	Change from EuroQol EQ-5D (EQ-5D-3L) to EuroQol EQ-5D-5L at baseline and all follow-up assessments.
5.5.4	29	Inclusion of minimisation with an 80% probabilistic element in the randomisation process.
5.6	30	Change initial follow-up with EuroQol EQ-5D(-5L) from 7 days post-procedure to 2 weeks post-procedure.
5.8	31	Clarification that in the event that a participant loses mental capacity during the trial, mortality data will continue to be collected from the Health and Social Care Information Centre in England and the corresponding agencies in the devolved nations, subject to the required regulatory approvals, and inclusion of the additional proposal to collect hospitalisation data, subject to the required regulatory approvals.
16	44	References updated.
19.7	65	Addition of patient resource-use questionnaire.
22	71	Schedule of Procedures updated to reflect amendments, as above.
Various		Minor amendments to clarify text, to expand the description of study procedures, and to correct typographical errors and punctuation.

24 INVESTIGATOR AGREEMENT

"I have read this protocol and agree to abide by all provisions set forth therein. I agree to adhere to the principles of the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice."

Principal Investigator (Print Name)	Investigator Signature	Date
Co-Investigator (Print Name)	Investigator Signature	Date
Co-Investigator (Print Name)	Investigator Signature	Date