Review protocol for transcatheter aortic valve implantation to treat aortic stenosis

ID	Field	Content
1.	Review title	What is the clinical and cost effectiveness of transcatheter aortic valve implantation for adults with aortic stenosis and for whom surgery presents a low or intermediate risk?
2.	Review question	What is the clinical and cost-effectiveness of TAVI compared to surgery for adults with aortic stenosis and for whom surgery presents a low or intermediate risk?
3.	Objective	To assess and compare the clinical and cost-effectiveness of transcatheter aortic valve implantation and surgery in adults with aortic stenosis requiring intervention
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies • Letters and comments are excluded The searches will have a cut-off date of 2021 The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diagnosed aortic stenosis in adults aged 18 years and over
6.	Population	Inclusion: Adults 18 years and over presenting with aortic stenosis requiring intervention, stratified by disease type as follows: Aortic stenosis • tricuspid • bicuspid Adults 18 years and over at low or intermediate surgical risk (as defined by the trial) Risk of surgery: STS PROM score: People have low surgical risk if they score less than 4%, intermediate risk if they score between 4% and 8% and high risk if they score more than 8%. Note: • A threshold of 75% will be used to assign studies to the above strata. For example, to be assigned to the aortic stenosis (bicuspid) stratum, 75% of the population of a study would have to have aortic stenosis (bicuspid). • Trials where patients have previously received medical management will be included. Trials with a mixed risk of surgery population will only be included if ≤10% are at high risk for surgery, these will be downgraded once for indirectness.

		Exclusion: • Children (aged <18 years). • Adults with congenital heart disease (excluding bicuspid aortic valves). • Adults with non-bicuspid or non-tricuspid aortic stenosis • Tricuspid stenosis, mitral value disease, aortic regurgitation and pulmonary valve disease. • Adults undergoing a second or greater number of surgical or transcatheter interventions for heart valve disease (exclude if ≥10% of one or more of the groups have had previous attempts at surgical or transcatheter management) • Adults with high risk of surgery (as defined by the trial)
7.	Intervention	• Transcatheter aortic valve implantation Exclusion: Valves no longer available: • ACURATE neo2 • Trilogy (Jenavalve) Trials will be included if at least 75% of the TAVI arm received a valve that is available Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest.
8.	Comparator	• Surgical aortic valve replacement Sutureless valves will be included Exclusion: Valves no longer available:

		• Trifecta Trials will be included if at least 75% of the surgical arm received a valve that is available
9.	Types of study to be included	• Randomised controlled trials (RCTs) or systematic reviews of RCTs If no RCT data are available, observational data will not be considered for this review. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.
10.	Other exclusion criteria	Exclusion criteria: • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Non-randomised studies / observational studies • Non-English language studies
11.	Context	N/A
12.	Primary outcomes	• All-cause mortality • Stroke Above outcomes will be pooled at the following time-points: • ≤30 days

		• > 30 days to 1 year • >1 to 5 years • > 5 years • Health-related quality of life (EQ-5D, MLHFQ, KCCQ - overall domains reported only) • Need for re-intervention • Onset or exacerbation of heart failure • Major bleeding (including life threatening, disabling bleeding, major bleeding) Above outcomes will be pooled at the following time-points: • ≤30 days • ≥1 year Where multiple follow-up time-points are reported within these categories, the latest time-point will be extracted. Outcomes measures taken at ≤30 days follow-up capture the intervention-related response. Dichotomous outcome data will be extracted as number of people with at least one event. Alongside event data, where available, HR data will also be extracted for the following three prioritised outcomes to inform the health economic model: • All-cause mortality • Stroke • Need for reintervention Agreed MID thresholds: • All-cause mortality*: o Clinical importance: 1 for RR (any change) o Imprecision: 0.9, 1.1 for RR • Stroke*:

		○ Clinical importance: 1 for RR (any change) ○ Imprecision: 0.9, 1.1 for RR • Health related quality of life scales: ○ Clinical importance and imprecision: EQ-5D 0.03 for MD, MLHFQ and KCCQ 5 for MD • Other dichotomous outcomes: ○ Clinical importance and imprecision: 0.9, 1.1 for RR Note: The MIDs stated above will be used for outcomes that are also reported as HR: All-cause mortality, Stroke and Need for reintervention * Any change for all-cause mortality and stroke outcomes was deemed clinically significant and therefore the line of no effect, 1 for RR and HR, was used as the MID when determining clinical importance. For the assessment of imprecision within the analyses, MIDs thresholds of 0.9 and 1.1 were applied consistently to all dichotomous and time-to-event outcomes, including all-cause mortality and stroke.
13.	Secondary outcomes	• Length of stay (initial intervention) (extracted at longest time-point reported) • Re-hospitalisation (extracted at longest time-point reported) • Intervention-related pacemaker implantation (≤1 year) • Acute kidney injury ≥stage 3/need for dialysis (≤1 year) • Major vascular complications (≤1 year) • Intervention-related atrial fibrillation (≤1 year) • Greater than mild paravalvular leak (≤1 year) • Structural valve deterioration (as defined by VARC 3) (extracted at longest time point reported) Where multiple follow-up time-points are reported, the latest time-point will be extracted. Dichotomous outcome data will be extracted as number of people with at least one event. Agreed MID thresholds to use for imprecision and clinical importance ratings:

		• All secondary dichotomous outcomes: 0.9, 1.1 for RR • Length of stay: 1 day for MD
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, study type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs The quality assessment will be performed by one reviewer and this will be quality assured by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using

		Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic, visual inspection of the point estimates and confidence intervals and take into account the sample size and SD of the studies in the meta-analysis. For specific details on how heterogeneity is interpreted, see the methods chapter of the guideline. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. Publication bias will be investigated using a funnel plot when there are 10 or more studies in an analysis. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group. Importance and imprecision of findings will be assessed against minimally important differences (MIDs).

17.	Analysis of sub-groups	**Evidence will be stratified by:**
		
		• Population – disease type:
		  ○ aortic stenosis (tricuspid)
		  ○ aortic stenosis (bicuspid)

		Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
		
		• Age (<70 vs. ≥70 years)
		• Male vs female
		• Invasiveness of procedure:
		  ○ Minimally invasive surgery replacement with biological or mechanical valves
		  ○ Standard surgery replacement with biological or mechanical valves
		• For surgical replacement (minimally invasive or standard), mechanical vs. biological valves
		• Different routes of transcatheter intervention (transfemoral, transapical and sub-clavian)
		• Risk of surgery: low risk vs intermediate risk
		• Valve generation: 1st generation vs 2nd/3rd generation
		
		Studies will be assigned to different subgroups using a threshold of 75% - for example, a study in which 80% of the population have transfemoral route of transcatheter intervention only and 20% transapical will be assigned to the transfemoral route group when subgrouping for this factor.
		
		Where evidence is stratified or subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic

		☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
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