Table 2: Review protocol: Monitoring in people with repaired or replaced heart valves

ID	Field	Content
0.	PROSPERO registration number	CRD42020162807
1.	Review title	Clinical protocol for monitoring in people with repaired or replaced heart valves
2.	Review question	What is the most clinically and cost-effective frequency of echocardiography or clinical review for monitoring in adults with repaired or replaced heart valves?
3.	Objective	To assess the clinical and cost-effectiveness of echocardiography or clinical monitoring at different frequencies in people with heart valve disease and repaired or replaced heart valves as frequency of follow-up varies across the country.
4.	Searches	The following databases from inception 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 • Human studies • Letters and comments are excluded Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the 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 heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion:

		Adults 18 years and over with heart valve disease and repaired or replaced heart valves, stratified by biological (including transcatheter) or mechanical valves and repair or replacement: • Repair • Replacement with biological valves • Replacement with homograft and autograft valves (including the Ross procedure) • Replacement with mechanical valves • Replacement with mixture of biological and mechanical valves (i.e. some in population with biological and some with mechanical) A threshold of 75% will be used to assign studies to the above strata. Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease.
7.	Intervention/ Test	Monitoring by echocardiography (transthoracic or transoesophageal) at various frequencies followed by appropriate valve re-do intervention: • More frequently than once a year (<12 months e.g. every 3 or 6 months) • Once a year (every 12 months) • Less frequently than once a year (>12 months; e.g. every 2, 3 or 5 years)
8.	Comparator/Reference standard/Confounding factors	Other active comparator listed above No monitoring/clinical review (echo only performed if new symptoms emerge/symptoms worsen)
9.	Types of study to be included	Randomised controlled trials (RCTs) and systematic reviews of RCTs. Published NMAs and IPDs will be considered for inclusion If insufficient[a] evidence is found from RCT, non-randomised studies will be considered for inclusion. Important confounders that NRS should be adjusted for: • Dialysis (haemodialysis or peritoneal dialysis) • Poor INR control • Endocarditis (provoking valve destruction earlier)
10.	Other exclusion criteria	Exclusion criteria: • Non-English language studies

[a] This will be assessed for each intervention separately. There is no strict definition, but in discussion with the GC we will consider whether we have enough to form the basis for a recommendation (e.g., one large well-conducted RCT, or more than one small RCT).

		• 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.
11.	Context	Current practice is to follow people up using echocardiography. However, the frequency of follow up in inconsistent across the country.
12.	Primary outcomes (critical outcomes)	• All-cause mortality • Cardiac mortality • Health-related quality of life • Stroke or TIA • Hospitalisation for heart failure or other cardiac event All outcomes to be measured at 6 months (when follow-up is more frequent than once a year) and ≥12 months (for all monitoring frequencies). Where multiple time-points are reported within a single study, the longest time-point only will be extracted.
13.	Secondary outcomes (important outcomes)	• New onset atrial fibrillation All outcomes to be measured at 6 months (when follow-up is more frequent than once a year) and ≥12 months. Where multiple time-points are reported within a single study, the longest time-point only will be extracted
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. An in-house developed database, EviBASE, will be used for data extraction and quality assessment of clinical studies. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Checklists used in this intervention review are as follows for different types of study design: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised study, including cohort studies: Cochrane ROBINS-I

		10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.	
16.	Strategy for data synthesis	• Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was 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 http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.	
17.	Analysis of sub-groups	**Subgroups that will be investigated if heterogeneity is present:** • Transcatheter vs. surgical intervention with biological valves • Type of valve repaired or replaced (aortic, mitral, tricuspid; stenosis and regurgitation can be combined as this has been corrected) • Number of valve interventions (1 vs >1 intervention on a particular valve) • Time since intervention (≤5 years vs > 5 years) Studies will be assigned to different subgroups using a threshold of 75%.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	09/05/2019	
22.	Anticipated completion date	17/06/2021	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑
		Risk of bias (quality) assessment	☑ / ☑
		Data analysis	☑ / ☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre	
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist]	

		Katie Broomfield [Project manager]	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	None	
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Aortic regurgitation; aortic stenosis; heart valve disease; heart valve repair; heart valve replacement; intervention; mitral regurgitation; mitral stenosis; monitoring; monitoring frequency; tricuspid regurgitation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk