Table 5: Review protocol: Monitoring of people with heart valve disease and no current indication for intervention

ID	Field	Content
0.	PROSPERO registration number	CRD42020162805
1.	Review title	Clinical protocol for monitoring of people with heart valve disease and no current indication for intervention.
2.	Review question	Where there is no current indication for intervention, what is the most clinically and cost-effective type and frequency of test for monitoring in adults with heart valve disease?
3.	Objective	To establish how often and with what test people with heart valve disease and no current indication for intervention should be assessed to determine the right timing for intervention before they have any major events. Current practice is to use echocardiography for follow-up but the frequency varies. The aim is to determine the optimal frequency of echo and whether any additional tests provide benefit in specific groups.
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 for MEDLINE database 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 aged 18 years and over with diagnosed heart valve disease and no current indication for intervention, stratified by the severity of valve disease as follows: • Mild • Moderate • Severe *Severity assessed by echo and rated as per* The British Society of Echocardiography. Other definitions will be accepted and downgrade for indirectness if appropriate. Exclusion: Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. People who have had prior heart valve repair or replacement (transcatheter or surgical).
7.	Intervention/ Test	Any of the following assessment strategies used for monitoring purposes, followed by appropriate valve intervention, in the specified population: Biomarkers (alone or in combination with echo): • BNP (B-type natriuretic peptide) • NT-proBNP (N-terminal prohormone brain natriuretic peptide) Imaging: • Echocardiography • CT (alone or in combination with echo) • CMR (cardiovascular magnetic resonance; alone or in combination with echo) Patient reported outcome measures (PROMS; alone or in combination with echo), including:

		• EuroQol • Minnesota Living With Heart Failure Questionnaire (MLHFQ) • Veterans Specific Activity Questionnaire Other methods: • Electrocardiogram (ECG) (alone or in combination with echo) • Clinical review only (no specific tests performed, as defined by the study authors) • Exercise testing (for example Bruce protocol; alone or in combination with echo) Different frequencies of the tests used for monitoring will be considered as separate interventions. Therefore, we will include studies comparing different frequencies of the same or different interventions. Frequency will be categorised into the following groups: • More frequently than once a year (e.g. every 3 or 6 months) • Once a year • Less frequently than once a year (e.g. every 2, 3 or 5 years) Each monitoring test is a different strata and each frequency is a sub-analysis for each test.
8.	Comparator/Reference standard/Confounding factors	Other active comparator listed above No monitoring (for example, tests 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 RCTs, non-randomised studies will be considered for inclusion. Important confounders NRS must be adjusted for:

[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 RCTs).

		• Coronary artery disease • Aortopathy in aortic valve disease
10.	Other exclusion criteria	Exclusion criteria: • Non-English language studies • 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 to monitor whether intervention has become necessary. However, the frequency of follow up is inconsistent across the country and other modalities of follow up are also being variably used.
12.	Primary outcomes (critical outcomes)	• All-cause mortality • Cardiac mortality • Health-related quality of life (any validated measure) • Hospitalisation for heart failure or other cardiac reason (e.g., for syncope in severe AS) If data are available, follow-up will be reported as a first preference at: • 12 months for mild and moderate valve disease • 6 months for severe valve disease. Where multiple time-points are reported within a single study, only the time-point closest to that stated above will be extracted.
13.	Secondary outcomes (important outcomes)	• New-onset atrial fibrillation If data are available, follow-up will be reported as a first preference at: • 12 months for mild and moderate valve disease • 6 months for severe valve disease. Where multiple time-points are reported within a single study, only the time-point closest to that stated above 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. A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary).	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Type of valve disease: aortic stenosis (bicuspid), aortic stenosis (non-bicuspid/calcific), aortic regurgitation (including bicuspid and non-bicuspid), mitral stenosis, mitral regurgitation, tricuspid regurgitation • Coronary artery disease • Aortopathy in aortic valve disease 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	N/A
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; 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	