Review protocol for cardiac MRI and CT in determining the need for intervention

ID	Field	Content
0.	PROSPERO registration number	CRD42020182863
1.	Review title	In adults with heart valve disease, what is the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?
2.	Review question	In adults with heart valve disease, what is the prognostic value and cost effectiveness of cardiac MRI and cardiac CT to determine the need for intervention?
3.	Objective	To assess the prognostic value of cardiac MRI and cardiac CT to determine the need for intervention in adults with diagnosed heart valve disease.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded • Date: exclude studies published before the year 1985 (for MR), and 1995 (for CT)

		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 (including bicuspid) regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with diagnosed heart valve disease **requiring further tests** after echocardiography to determine whether intervention is needed. Data will be stratified by the type of heart valve disease as follows: • aortic [including bicuspid] stenosis • aortic [including bicuspid] regurgitation • mitral stenosis • mitral regurgitation • tricuspid regurgitation Inclusion of indirect evidence: Studies including mixed populations will be included (and downgraded for indirectness) if >75% of the included patients meet the protocol criteria. Exclusion:

		Children aged less than 18 years. Adults with congenital heart disease (excluding bicuspid aortic valves). Tricuspid stenosis and pulmonary valve disease. Adults with previous intervention for HVD (surgical or transcatheter).
7.	Predictors/prognostic factors of need for intervention	**A. Cardiac MRI** **Mitral regurgitation** **Primary mitral regurgitation** • left ventricular systolic function based on ejection fraction <50% or <60% • left atrial dimensions (volume / volume index) ≥60 mL/m^2 BSA • Quantity of MR (regurgitant fraction or volume in ml – no accepted threshold, suggestion RF 40 or 50% and RV of 55 or 60 ml) **Secondary mitral regurgitation** • left ventricular systolic function based on ejection fraction <20% **Aortic stenosis** • left ventricular systolic function based on ejection fraction <50% or <60% • Myocardial fibrosis (late gadolinium enhancement) (present or not in a pattern consistent with aortic stenosis, or infarction) • Aortic valve area (<0.6cm^2/m^2 or <0.8 or 1.0 cm^2) **Aortic regurgitation** • left ventricular systolic function based on ejection fraction <50% or <60% • Quantity of AR (regurgitant fraction or volume in ml – no accepted threshold, suggestion RF 30 or 40% and RV of 55 or 60 ml) • Presence of holodiastolic flow reversal in the descending aorta

		Mitral stenosis • Valve area by direct planimetry <1.0cm^2 **Tricuspid regurgitation (isolated)** • reduced right ventricular systolic function – no thresholds • increasing right ventricular dimensions – no thresholds (dilated – mild, moderate, severe) • Regurgitant orifice area **B. Aortic size on cardiac MRI or CT** **Aortic stenosis or aortic regurgitation** • Bicuspid: aorta > 5cm or > 5.5cm • Tricuspid: aorta > 5.5cm **C. Cardiac CT** **Primary or secondary mitral regurgitation** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels • Severity of mitral annular calcification (mild, moderate, severe) **Aortic stenosis** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels • Aortic valve area (<0.6cm^2/m^2 or <0.8 or 1.0 cm^2) • Calcium score of aortic valve (threshold > 2000 AU for men and >1200 AU for women) **Aortic regurgitation** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels **Mitral stenosis**

		• CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels • Valve area by direct planimetry <1.0cm^2 • Severity of mitral valve or annular calcification (mild, moderate, severe) **Tricuspid regurgitation** • CT coronary angiogram: mild, moderate, or severe coronary disease of 1,2 or 3 vessels
8.	Confounding factors	For non-operative mortality • Age • Smoking For hospital admission for heart failure or unplanned intervention and for reduced cardiac function in those without intervention: • Age For post-operative mortality: • Age For all outcomes relating to cardiac calcium score in patients with aortic stenosis: • Age • Smoking For all other outcomes • No known confounders
9.	Types of study to be included	• Prospective and retrospective cohort studies that control for confounders in the study design or analysis will be included preferentially

		• If no controlled studies are identified, unadjusted cohort studies will be considered for inclusion. This will be assessed separately for each test and population. • Systematic reviews of the above • If no cohort studies are identified case control studies will be considered for inclusion, but downgraded for risk of bias. This will be assessed separately for each test and population.
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-English language studies
11.	Context	Among adults with diagnosed heart valve disease who have had an initial echocardiography assessment, some require further tests to determine if intervention is needed. CT and MRI may be used in this population to provide additional information on the severity of the disease.
12.	Primary outcomes (critical outcomes)	Indication for intervention based on prognosis for the following without intervention: • Mortality (1 and 5 years) • Hospital admission for heart failure or unplanned intervention (1 and 5 years) • Reduced cardiac function (echo parameters – LVEF) 1 and 5 years • Symptom onset or symptom worsening (e.g. that led to surgery being required) 1 and 5 years Indication for intervention based on predictors of the following post-operative outcomes: • Mortality (6 and 12 months) • Hospital admission for heart failure (6 and 12 months)

		• Reduced cardiac function (echo or CMR parameters – for example LVEF <50%) (6 and 12 months) • Return to normal LV volumes post-operatively based on echo or CMR as defined in the study (6 and 12 months) • >20% reduction in LV volume post-operatively based on echo or CMR (6 and 12 months) This may be reported as an adjusted HR, RR or OR. Sensitivity, specificity and AUC will not be included as these do not allow for multivariable adjustment. Use the time point closest to each of the listed endpoints and combine data as follows: 6 months: include 0-6 months 12 months: include >6 months up to 12 months 1 year: include 0-12 months 5 years: include all >1 year. No minimum follow-up.
13.	Secondary outcomes (important outcomes)	N/A
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. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). This will include study design, analysis method, population source, baseline population characteristics, confounding

		factors accounted for, numbers in each prognostic group, numbers of events, and calculated effect estimate when reported.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • The QUIPS checklist will be used to assess risk of bias of each individual study. 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	• Pooling will be considered if the population, prognostic factor, outcomes, confounders and analysis are sufficiently similar. It is not necessary for the exact same confounders to be adjusted for because only the key confounders, with higher coefficients of determination, will noticeably affect the effect size. Many of the other confounders will have a relatively small effect on the point estimate so it may be appropriate to pool studies with slightly different arrays of confounding variables. This is judged on a case-by-case basis. • Where data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome. • Data from the meta-analysis will be presented and quality assessed in adapted GRADE tables 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 risk factor. Publication or other bias will be tested for when there are 5 or more studies for an outcome. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. We will conduct sensitivity analyses 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 using random-effects. • If meta-analysis is not possible or appropriate, results will be reported individually per outcome in adapted GRADE tables. 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	**Groups that will be analysed separately (strata):** Stratified by the presence or absence of symptoms and the type of heart valve disease as follows: ○ aortic [including bicuspid] stenosis ○ aortic regurgitation ○ mitral stenosis ○ mitral regurgitation ○ tricuspid regurgitation **Subgroups that will be investigated if heterogeneity is present:** • none identified	
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; cardiac computerised tomography; cardiac magnetic resonance imaging; diagnosis; heart valve disease; mitral regurgitation; mitral stenosis; prognosis; 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	