National Institute for Health and Care Excellence

Final

Heart valve disease presenting in adults: investigation and management

[K] Evidence review for monitoring in people with repaired or replaced heart valves

NICE guideline NG208

Intervention evidence review underpinning recommendation 1.8.1 and the research recommendation in the NICE guideline

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Final draft

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1 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?

1.2 Introduction

Repaired or replaced heart valves may fail or degenerate, developing progressive clinical and haemodynamic consequences that lead to a need for reintervention. However, the progression to a need for reintervention is usually slow and predictable. It is important to determine the most clinically and cost-effective frequency of echocardiography or clinical review for monitoring of repaired or replaced heart valves.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

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.
Interventions/tests	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)
Comparisons	Other active comparator listed above No monitoring/clinical review (echo only performed if new symptoms emerge/symptoms worsen)
Outcomes	Primary outcomes: • All-cause mortality • Cardiac mortality

	• Health-related quality of life • Stroke or TIA • Hospitalisation for heart failure or other cardiac event Secondary 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 (for all monitoring frequencies). Where multiple time-points are reported within a single study, the longest time-point only will be extracted.
Study design	Randomised controlled trials (RCTs) and systematic reviews of RCTs. Published NMAs and IPDs will be considered for inclusion If insufficient evidence is found from RCT, non-randomised studies (NRS) 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)

1.4 Clinical evidence

1.4.1 Included studies

Searches were performed for both randomised controlled trials and observational studies matching the protocol. However, no relevant clinical studies comparing different frequencies of echocardiography monitoring following valve intervention were identified for any of the listed strata.

One retrospective audit of the follow-up practice of those that had undergone surgical heart valve repair or replacement at a UK tertiary centre was identified,[1] which compared practice at the centre with existing European guidelines. Although mortality between those with yearly follow-up and those without yearly follow-up could be calculated from the information presented, no adjustment was performed for any confounding factors and baseline characteristics within the two groups were not reported. Therefore this study was not included in the review but was noted as a relevant source concerning current practice for monitoring of those with repaired or replaced valves in the UK.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E:and GRADE tables in Appendix F:.

1.4.2 Excluded studies

See the excluded studies list in Appendix I:.

1.4.3 Summary of clinical studies included in the evidence review

No clinical evidence was identified for this review.

1.4.4 Quality assessment of clinical studies included in the evidence review

No clinical evidence was identified for this review.

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Summary of studies included in the economic evidence review

No economic studies were included

1.6 Evidence statements

1.6.1 Clinical evidence statements

No clinical evidence was identified.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Outcomes considered to be critical as listed in the protocol were all-cause mortality, cardiac mortality, health-related quality of life, stroke or TIA and hospitalisation for heart failure or other cardiac event.

One additional outcome of new-onset atrial fibrillation was included as an important outcome.

It was agreed that in terms of time-points for outcome reporting, where possible, all outcomes should be reported 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 would be extracted.

The outcome of stroke or TIA was included in this review but not in the other monitoring review as stroke and TIA is more of an issue once intervention has been performed on the valve.

1.7.1.2 The quality of the evidence

No clinical evidence was included in the review.

1.7.1.3 Benefits and harms

In the absence of any evidence matching the protocol for this review, the committee discussed current practice with regards to the frequency of echocardiography performed following valve intervention and used this to inform a consensus recommendation.

The committee noted that current practice for those that had received valve repair or replacement was variable and depends on patient factors, such as comorbidities and the shape of the heart due to either other cardiac disease or previous cardiac operations, as well as the type of procedure that has been performed (repair or replacement).

In addition, the type of valve used if replacement was performed is also a factor that means follow-up frequency post-intervention varies. The committee agreed that the durability of mechanical valves is considered to be very good and the risk of needing a redo operation due to valve failure following the operation is low, whereas bioprosthetic valves have a lower durability and deterioration may occur within 10 years. Due to this, the committee noted that in some cases mechanical valves may be monitored initially over the first 12 months and then not followed up regularly unless any problems develop, but that practice was variable

for mechanical valve monitoring. However, with bioprosthetic valves monitoring would usually be performed more often – though the committee noted that the frequency of follow-up for those with bioprosthetic valves does vary in practice, with examples including, but not limited to, follow-up annually starting from the year of the operation and others starting annual follow-up of the valves once 5 years has passed.

It was also agreed that any concerns about abnormal valve function or consequences of the procedure, for example paravalvular leak, may also affect the frequency of monitoring, as if there are existing concerns then follow-up may be performed more often than for those where there are no current concerns about the valve function or consequences of the procedure.

The committee also noted the potential effects that the frequency of follow-up can have on patients and that it should be discussed with the patient. For example, follow-up more frequently could increase the anxiety of some patients as they feel they are not able to go about their life without thinking about their condition for a substantial period of time, while for others more frequent follow-up may help to ease any concerns they have about their condition.

The committee agreed that despite the monitoring frequency agreed upon, it is important to encourage patients who feel that their condition has deteriorated to seek further review and arrange for a follow-up sooner. In addition, the committee noted that follow-up for other concomitant cardiac conditions should be performed as appropriate.

Overall, in terms of current practice, the committee agreed that practice was variable and used this to develop a consensus recommendation for the monitoring of those with repaired or replaced heart valves. This recommendation did not specify a frequency at which follow-up should be performed but that the decision should be based on the durability of the prosthetic valve or of the result of the repair, the presence of another condition, including other heart disease, residual valve abnormality or consequences of the procedure (for example, paravalvular leak), concerns about abnormal valve function and the patient's wishes, as described in detail in the previous paragraphs. The recommendation also states that people and their family or carers should be advised to seek advice if their heart condition deteriorates in between scheduled follow-up appointments. The need for ongoing surveillance should be shared with the patient and relevant health care professionals as part of good clinical practice.

To address the lack of evidence the committee made a research recommendation (see Appendix J.1 for details) on the monitoring after different type of valve interventions including repair and replacement with tissue or mechanical valves.

Evidence from expert testimony to cover the population of pregnant women or women of childbearing age indicated that monitoring of pregnant women may be different in terms of the frequency and type of monitoring required, which is covered by a recommendation discussed in evidence review A about referring to a cardiologist with expertise in the care of pregnant women if they have moderate or severe valve disease, bicuspid aortic valve disease of any severity and associated aortopathy, or a mechanical prosthetic valve.

1.7.2 Cost effectiveness and resource use

No health economic evidence was identified for this question.

The committee made a consensus recommendation to alert clinicians of the common factors that need to be taken into account when deciding on the frequency and type of monitoring for patients with a repaired or replaced heart valve. The committee noted that this recommendation is in line with current practice and does not necessary change the monitoring for this population and therefore unlikely to have a substantial resource impact.

1.8 Recommendations supported by this evidence review

This evidence review supports recommendation 1.8.1 and the research recommendation on monitoring after an intervention.

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Appendices

Appendix A: Review protocols

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

Table 3: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[40] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Heart valve disease – search strategy 11 - monitoring of people with heart valve disease and no current indication for intervention AND monitoring in people with repaired or replaced heart valves

This literature search strategy was used for the following reviews:

- 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?
- What is the most clinically and cost-effective frequency of echocardiography or clinical review for monitoring in adults with repaired or replaced heart valves?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[40]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/

21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	exp Natriuretic Peptide, Brain/
37.	Biomarker*.ti,ab.
38.	((brain or b-type) adj2 natriuretic peptide*).ti,ab.
39.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
40.	exp Echocardiography/
41.	(Echo* or transoesophageal or transesophageal or transthoracic or TOE or TEE or TTE).ti,ab.
42.	exp Electrocardiography/
43.	(electrocardio* or ECG or EKG).ti,ab.
44.	exp Tomography, X-Ray computed/
45.	(comput* adj2 tomograp*).ti,ab.
46.	(CT adj3 (cine or CAT or scan* or x ray* or xray* or imag*)).ti,ab.
47.	exp Magnetic Resonance Imaging/
48.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
49.	((cardiac or cardiovascular) adj mr).ti,ab.
50.	(mri* or nmr* or cmr*).ti,ab.
51.	patient reported outcome measures/
52.	("patient reported outcome measures" or PROM*).ti,ab.
53.	(euroqol* or eq5d* or eq 5*).ti,ab.
54.	("minnesota living with heart failure questionnaire" or MLHFQ or MLWHF).ti,ab.
55.	("Veterans Specific Activity Questionnaire" or VSAQ).ti,ab.
56.	(clinic* adj2 (assess* or general or special* or valve* or monitor* or examin*)).ti,ab.
57.	Exercise tolerance/ or Exercise Test/
58.	((physical* or exercise* or fitness) adj5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera* or test*)).ti,ab.
59.	(stress test adj2 (cardiac or ECG)).ti,ab.
60.	bruce protocol.ti,ab.
61.	or/36-60
62.	Meta-Analysis/

63.	exp Meta-Analysis as Topic/
64.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
65.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
66.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
67.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
68.	(search* adj4 literature).ab.
69.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
70.	cochrane.jw.
71.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
72.	or/62-71
73.	randomized controlled trial.pt.
74.	controlled clinical trial.pt.
75.	randomi#ed.ti,ab.
76.	placebo.ab.
77.	randomly.ti,ab.
78.	Clinical Trials as topic.sh.
79.	trial.ti.
80.	or/73-79
81.	Epidemiologic studies/
82.	Observational study/
83.	exp Cohort studies/
84.	(cohort adj (study or studies or analys* or data)).ti,ab.
85.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
86.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
87.	Controlled Before-After Studies/
88.	Historically Controlled Study/
89.	Interrupted Time Series Analysis/
90.	(before adj2 after adj2 (study or studies or data)).ti,ab.
91.	or/81-90
92.	35 and 61 and (72 or 80 or 91)

Embase (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.

7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	exp brain natriuretic peptide/
35.	Biomarker*.ti,ab.
36.	((brain or b-type) adj2 natriuretic peptide*).ti,ab.
37.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
38.	exp Echocardiography/
39.	(Echo* or transoesophageal or transesophageal or transthoracic or TOE or TEE or TTE).ti,ab.
40.	exp electrocardiography/
41.	(electrocardio* or ECG or EKG).ti,ab.
42.	exp x-ray computed tomography/
43.	(comput* adj2 tomograp*).ti,ab.
44.	(CT adj3 (cine or CAT or scan* or x ray* or xray* or imag*)).ti,ab.
45.	exp nuclear magnetic resonance imaging/
46.	((magnetic or nuclear) adj2 resonance adj3 imag*).ti,ab.
47.	((cardiac or cardiovascular) adj mr).ti,ab.
48.	(mri* or nmr* or cmr*).ti,ab.
49.	exp patient-reported outcome/

50.	("patient reported outcome measure*" or PROM*).ti,ab.
51.	(euroqol* or eq5d* or eq 5*).ti,ab.
52.	("minnesota living with heart failure questionnaire" or MLHFQ or MLWHF).ti,ab.
53.	("Veterans Specific Activity Questionnaire" or VSAQ).ti,ab.
54.	(clinic* adj2 (assess* or general or special* or valve* or monitor* or examin*)).ti,ab.
55.	Exercise tolerance/ or Exercise Test/
56.	((physical* or exercise* or fitness) adj5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera* or test*)).ti,ab.
57.	(stress test adj2 (cardiac or ECG)).ti,ab.
58.	bruce protocol.ti,ab.
59.	or/34-58
60.	systematic review/
61.	meta-analysis/
62.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
63.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
64.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
65.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
66.	(search* adj4 literature).ab.
67.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
68.	cochrane.jw.
69.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
70.	or/60-69
71.	random*.ti,ab.
72.	factorial*.ti,ab.
73.	(crossover* or cross over*).ti,ab.
74.	((doubl* or singl*) adj blind*).ti,ab.
75.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
76.	crossover procedure/
77.	single blind procedure/
78.	randomized controlled trial/
79.	double blind procedure/
80.	or/71-79
81.	Clinical study/
82.	Observational study/
83.	family study/
84.	longitudinal study/
85.	retrospective study/
86.	prospective study/
87.	cohort analysis/
88.	follow-up/
89.	cohort*.ti,ab.
90.	88 and 89

91.	(cohort adj (study or studies or analys* or data)).ti,ab.
92.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
93.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	(before adj2 after adj2 (study or studies or data)).ti,ab.
95.	or/81-87,90-94
96.	33 and 59 and (70 or 80 or 95)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#2.	MeSH descriptor: [Heart Valves] explode all trees
#3.	((primary or secondary) NEXT valv* disease*):ti,ab
#4.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#5.	((mitral or aortic or tricuspid or pulmon*) NEXT (valv* or flap* or leaflet*) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#6.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#7.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#9.	valve-in-valve:ti,ab
#10.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#11.	MeSH descriptor: [Heart Murmurs] explode all trees
#12.	((heart or cardiac) NEXT murmur*):ti,ab
#13.	(or #1-#12)
#14.	MeSH descriptor: [Natriuretic Peptide, Brain] explode all trees
#15.	Biomarker*:ti,ab
#16.	((brain or b-type) near/2 natriuretic peptide*):ti,ab
#17.	(bnp or nt-probnp or nt-pro bnp or nt-bnp):ti,ab
#18.	MeSH descriptor: [Echocardiography] explode all trees
#19.	(electrocardio* or ECG or EKG):ti,ab
#20.	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#21.	(comput* near/2 tomograp*):ti,ab
#22.	(CT near/3 (cine or CAT or scan* or x ray* or xray* or imag*)):ti,ab
#23.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#24.	((magnetic or nuclear) near/2 resonance near/3 imag*):ti,ab
#25.	((cardiac or cardiovascular) near/1 mr):ti,ab
#26.	(mri* or nmr* or cmr*):ti,ab
#27.	MeSH descriptor: [Patient Reported Outcome Measures] explode all trees
#28.	("patient reported outcome measures" or PROM).ti,ab
#29.	(euroqol* or eq5d* or eq 5*):ti,ab
#30.	("minnesota living with heart failure questionnaire" or MLHFQ or MLWHF):ti,ab
#31.	("Veterans Specific Activity Questionnaire" or VSAQ).ti,ab

#32.	(clinic* near/2 (assess* or general or special* or valve or monitor* or examin*)):ti,ab
#33.	MeSH descriptor: [Exercise Tolerance] explode all trees
#34.	MeSH descriptor: [Exercise Test] explode all trees
#35.	((physical* or exercise* or fitness) near/5 (fit* or train* or therap* or activ* or strength or endur* or exert* or capacit* or tolera* or test*)):ti,ab
#36.	("stress test" near/2 (cardiac or ECG)):ti,ab
#37.	bruce protocol:ti,ab
#38.	(OR #14-#37)
#39.	#13 and #38

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.

13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/
38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/
41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51

53.	35 and 52

Embase (Ovid) search terms

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/

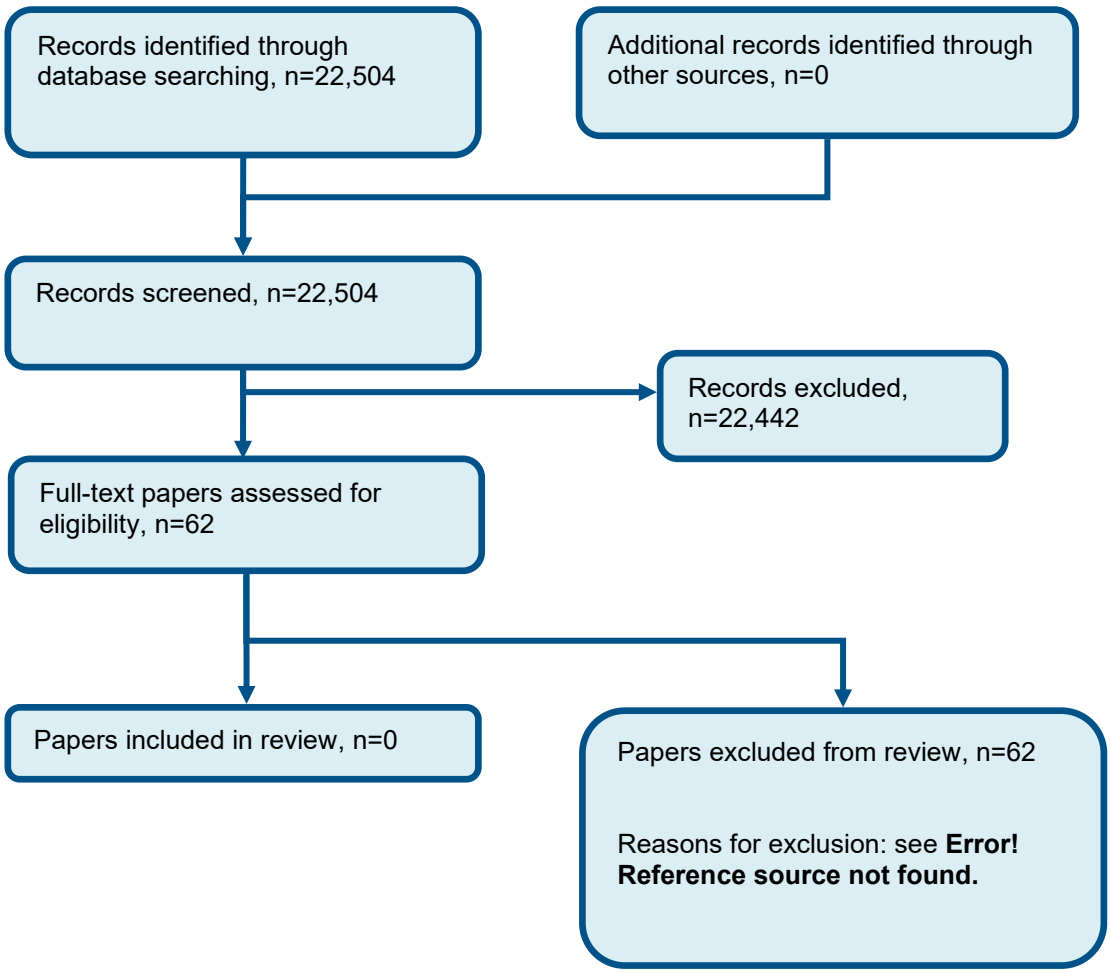
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of monitoring in people with repaired or replaced heart valves



Appendix D: Clinical evidence tables

No clinical evidence was identified for this review.

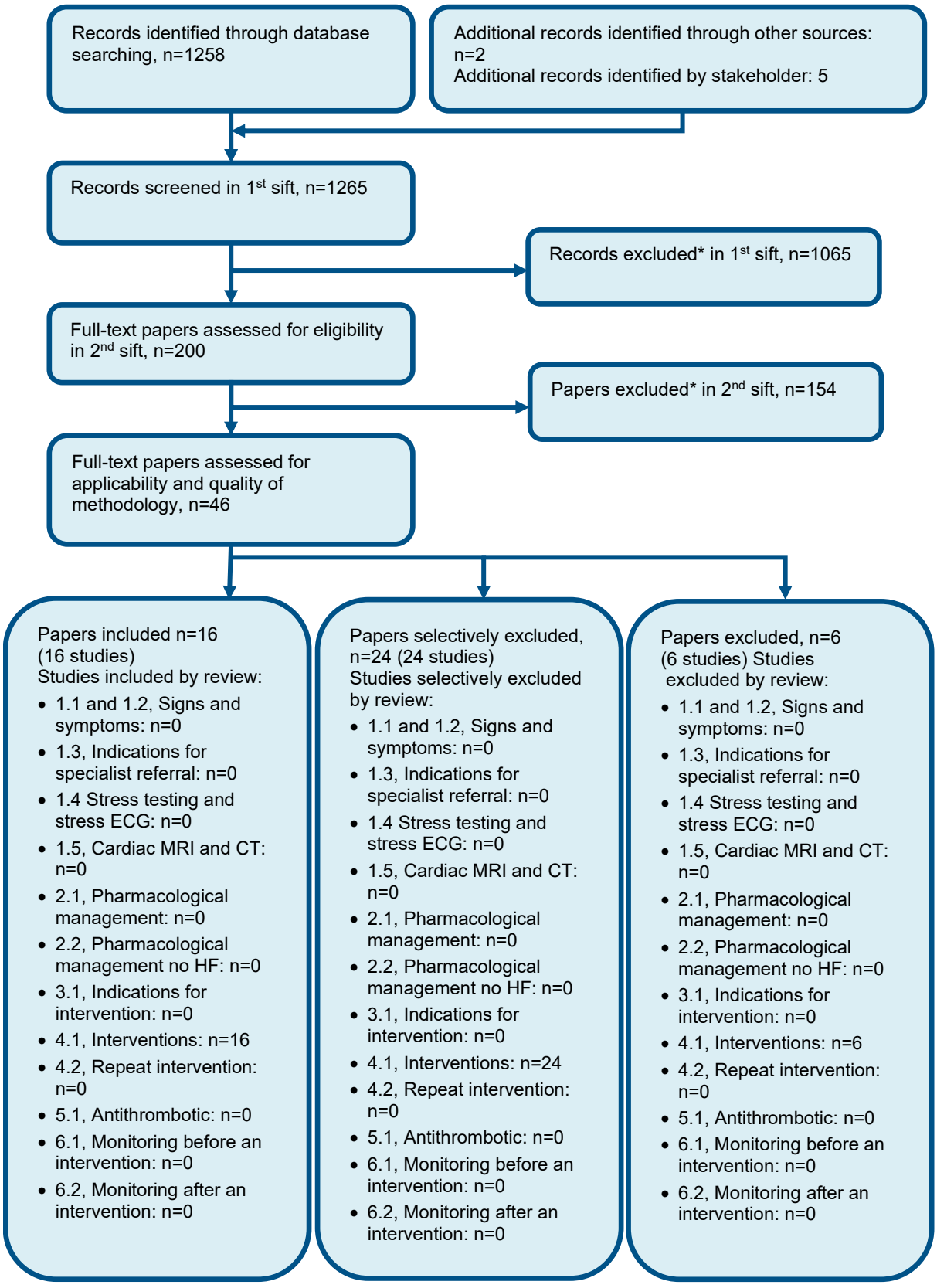
Appendix E: Forest plots

No clinical evidence was identified for this review.

Appendix F: GRADE tables

No clinical evidence was identified for this review.

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

No economic studies have been identified

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 6: Studies excluded from the clinical review

Study	Exclusion reason
Alaour 2018[1]	Incorrect study design: non-randomised with no adjustment for confounders
Alsaddique 2016[2]	Not guideline condition. Inappropriate comparison. No suitable outcomes
Black 1983[3]	Inappropriate comparison. Incorrect interventions
Borregaard 2019[4]	Inappropriate comparison. Incorrect interventions
Cheng 2008[5]	Incorrect study design: narrative review
Cho 2015[6]	Inappropriate comparison. Incorrect interventions
Choi 2018[7]	Inappropriate comparison. Incorrect interventions
Collas 2015[8]	Inappropriate comparison. Incorrect interventions
Drury 1987[9]	Inappropriate comparison. Incorrect interventions
Egbe 2018[10]	Inappropriate comparison. Incorrect interventions
Ellis 1995[11]	Inappropriate comparison. Incorrect interventions
Fraser 1992[12]	Incorrect study design: narrative review
Fritzsche 2005[14]	Inappropriate comparison. Incorrect interventions
Fritzsche 2007[13]	Inappropriate comparison. Incorrect interventions
Fritzsche 2007[15]	Incorrect interventions. Inappropriate comparison
Gallo 2020[16]	Incorrect study design: narrative review
Gerber 2019[17]	Inappropriate comparison. Incorrect interventions
Gillham 2007[18]	Incorrect interventions. Inappropriate comparison
Goncalves 2017[19]	Incorrect interventions. Inappropriate comparison
Greffe 2008[20]	Inappropriate comparison. Incorrect interventions
Gripari 2018[21]	Inappropriate comparison. Incorrect interventions. No suitable outcomes
Hansson 2013[22]	Inappropriate comparison. Incorrect interventions
Horstkotte 2016[23]	Incorrect interventions. Inappropriate comparison. No suitable outcomes
Hulshof 2019[24]	Inappropriate comparison. Incorrect interventions
Ikaheimo 1977[25]	Inappropriate comparison. Incorrect interventions
Jilaihawi 2012[26]	Inappropriate comparison. Incorrect interventions
Johl 2017[27]	Incorrect interventions. Inappropriate comparison
Katsanos 2015[28]	Inappropriate comparison. Incorrect interventions
Lee 2015[29]	Inappropriate comparison. Incorrect interventions
Leitch 1991[30]	Not review population. Inappropriate comparison. Incorrect interventions
Levy 2004[31]	Inappropriate comparison. Incorrect interventions
Lie 2017[32]	Incorrect interventions

Study	Exclusion reason
Lund 2003[33]	Inappropriate comparison. No suitable outcomes
Mastoris 2014[34]	Systematic review is not relevant to review question or unclear PICO
Mccrindle 1991[35]	Tricuspid stenosis and pulmonary valve disease. Adults with congenital heart disease (excluding bicuspid aortic valves).
Mclachlan 2015[36]	Inappropriate comparison. Incorrect interventions
Melacini 1993[37]	Inappropriate comparison
Melan 2013[38]	Inappropriate comparison. Incorrect interventions
Nanda 1991[39]	Incorrect study design: narrative review
Ozkan 2011[41]	Incorrect interventions. No suitable outcomes
Papanastasiou 2019[42]	Inappropriate comparison. Incorrect interventions. No suitable outcomes
Parpiyev 2011[43]	Inappropriate comparison. Incorrect interventions
Parro 2004[44]	Incorrect study design
Pislaru 2016[45]	Incorrect study design: narrative review
Ramondo 1991[46]	Incorrect interventions: monitoring during procedure rather than as follow-up after procedure
Reid 1991[47]	Incorrect study design: narrative review
Roudaut 1992[48]	Incorrect study design: narrative review
Singh 2009[49]	Inappropriate comparison. Incorrect interventions. No suitable outcomes
Sinning 2017[50]	Incorrect interventions. Inappropriate comparison
Sokalskis 2017[51]	Incorrect study design: narrative review
Soon 2017[52]	Incorrect study design: narrative review
Soschynski 2018[53]	Incorrect study design: narrative review
Stassano 1993[54]	Inappropriate comparison. Incorrect interventions
Sucha 2015[56]	Incorrect study design: narrative review
Sucha 2016[55]	Incorrect study design: narrative review
Symersky 2009[57]	Inappropriate comparison. Incorrect interventions
Tanguturi 2017[58]	Inappropriate comparison. Incorrect interventions. No suitable outcomes
Teeter 2017[59]	Inappropriate comparison. Incorrect interventions
Tsai 2009[60]	Incorrect interventions. Inappropriate comparison
Varma 2005[61]	Inappropriate comparison. Incorrect interventions
Weintraub 1990[62]	Inappropriate comparison. Incorrect interventions
Wood 2009[63]	Inappropriate comparison. Incorrect interventions

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 7: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J: Research recommendations

J.1 Monitoring after intervention

J.1.1 Research recommendation

What is the most clinically and cost-effective type and frequency of follow-up for different types of valve interventions, including repair and replacement with tissue or mechanical valves?

J.1.2 Why this is important

Currently, the follow-up of patients after valve interventions varies widely. Some patients are followed up every year (often with repeat echocardiography) indefinitely, while others are discharged without any follow-up (unless symptoms recur), and there are many examples between these extremes. Because future valve interventions (after a first intervention) carry a much higher risk, very few (if any) asymptomatic patients undergo second time ('re-do') interventions, so the benefit of follow-up in patients who remain asymptomatic following their first intervention is unclear. Different types of valve intervention also likely require different follow-up, given the very different durability of the various interventions. Understanding the best type and frequency of follow-up for patients following heart valve interventions would greatly aid clinical management.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	If the best type and frequency of follow-up after heart valve intervention could be determined, patients could receive the most appropriate frequency of follow-up. This would enable the identification of patients likely to benefit from further intervention, with improvement in their subsequent symptoms, whilst avoiding unnecessary follow-up in others.
Relevance to NICE guidance	No evidence was found for the frequency of monitoring after an intervention for heart valve disease. Current practice for those that had received valve repair or replacement is variable and depends on patient factors, such as comorbidities and the shape of the heart due to either other cardiac disease or previous cardiac operations, as well as the type of procedure that has been performed (repair or replacement). Research would enable stronger recommendations to be made on the frequency of monitoring.
Relevance to the NHS	Research in this area would inform NICE recommendations on the frequency and type of follow-up required for patients. If regular follow-up (and the optimal timing of this) resulted in improved outcomes, this would standardise the approaches to follow-up in the NHS.

	If reduced or no follow-up for some patients was shown to be as effective as more frequent follow-up, this would deliver major advantages in resource use, and avoid unnecessary appointments / tests.
National priorities	None known
Current evidence base	No evidence was found for the frequency of monitoring after an intervention for heart valve disease.
Equality considerations	None known

J.1.4 Modified PICO table

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) Exclusion: • Children aged less than 18 years. • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease.
Intervention	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)
Comparator	Other active comparator listed above No monitoring/clinical review (echo only performed if new symptoms emerge/symptoms worsen)
Outcome	<u>Primary outcomes</u> All-cause mortality; Cardiac mortality; Health-related quality of life; Stroke or TIA and hospitalisation for heart failure or other cardiac event <u>Secondary outcomes</u>

	New-onset atrial fibrillation
Study design	Adequately powered randomised controlled trial (ideally)
Timeframe	Long term
Additional information	None