Table 10: Review protocol: Clinical protocol for anticoagulant and/or antiplatelet therapy for biological prosthetic valves

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	5.1 What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?
2.	Review question	What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?
3.	Objective	To assess and compare the clinical and cost-effectiveness of anticoagulant and/or antiplatelet therapy in people with biological prosthetic valves as a result of transcatheter or surgical intervention, and with repaired valves after surgical intervention.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded

		• Validated study filters for systematic reviews and RCTs • No date restrictions applied Other searches: • Inclusion lists of 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 aged 18 years and over with repaired valves or biological prosthetic valves stratified by type of intervention: • transcatheter replacement • surgical replacement. • transcatheter repair • surgical repair Exclusion: • Children (aged <18 years) • Adults with congenital heart disease (excluding bicuspid aortic valves) • Tricuspid stenosis and pulmonary valve disease • Adults who have had a mechanical valve replacement
7.	Intervention/Exposure/Test	Oral anticoagulation therapy: • Vitamin K Antagonists (including: warfarin, acenocoumarol and phenindione) • Direct acting oral anticoagulants (DOACs) (including: dabigatran, rivaroxaban, apixaban and edoxaban)

		Oral antiplatelet therapy: • Single therapy (including aspirin, clopidogrel, ticagrelor and prasugrel) • Dual therapy (the combination of aspirin with either clopidogrel, ticagrelor or prasugrel). Combined oral anticoagulation and oral antiplatelet therapy A class effect will be used for analysis, combining all interventions within each drug class listed above. Warfarin will be analysed separately to DOACs, single antiplatelet therapy will be analysed separately to dual antiplatelet therapy. Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest.
8.	Comparator/Reference standard/Confounding factors	Other active comparator listed above. Placebo. No treatment or standard care (for example, treatment with all other required medication post-valve replacement apart from anticoagulants/antiplatelets).
9.	Types of study to be included	Randomised control trials (RCTs) or systematic reviews of RCTs. If no RCT data are available, observational data will not be considered. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.
10.	Other exclusion criteria	Exclusion criteria: • Crossover studies will not be included as variations in coagulation propensity will occur over the follow-up period which would make interventions non-comparable. • 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. • Studies including any participants with mechanical valves. • Non-randomised studies/observational studies. • Non-English language studies.
11.	Context	N/A.
12.	Primary outcomes (critical outcomes)	• All-cause mortality (dichotomous)

		• Health-related quality of life (continuous) • Major bleeding (dichotomous) • Minor bleeding (dichotomous) • Arterial thromboembolic events (dichotomous) Follow-up: All outcomes reported within the following time points will be pooled. The latest time points in each category will be used if multiple time points are reported in a single study. The categories include: • Short-medium term: ≤12 months • Long term: >12 months.
13.	Secondary outcomes (important outcomes)	• Hospital re-admission at 12 months (dichotomous). • Withdrawal due to adverse events at 12 months (dichotomous). • Thrombus on imaging at <12 months (dichotomous). • Need for reintervention at medium term (6 months to 12 months) and long term (>12 months) (time-to-event). • Valve degeneration (mean transvalvular gradient) at ≥12 months (continuous).
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. An in-house developed database; EviBase, will be used for data extraction. 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, participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; and critical appraisal ratings. 10% of the sifting and extractions will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third party.

		MS Excel will be used for data extraction and critical appraisal for health economic studies.
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) A 10% sample of the risk of bias assessments will be independently quality assured by a second reviewer. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third party 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. We will consider an I^2 value greater than 50% 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 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. • WinBUGS will be used for network meta-analysis, if possible given the data identified. A network meta-analysis will be considered if sufficient evidence is available to form a network. • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If significant heterogeneity is detected during meta-analysis, subgroups will be analysed. Subgroups were selected before initial searches were completed, and are listed in section 17 of this appendix. 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).

		Groups from the equality impact assessment were considered. It was decided that, while anticoagulation in women of childbearing age and pregnant women with prosthetic heart valves is of importance, they will not be considered separately in this question. This is as they are likely to have received mechanical prostheses instead of biological and so fall outside of the scope of the question.	
17.	Analysis of sub-groups	• Age (<75 versus ≥75) • Sex (male versus female) • Renal function (normal versus abnormal [as defined by individual studies]) • Hepatic function (normal versus abnormal [as defined by individual studies]) • Atrial fibrillation (atrial fibrillation versus no atrial fibrillation) • Replaced/repaired valve location (aortic, mitral or tricuspid) Studies will be assigned to different subgroups using a threshold of 75% - for example, a study in which 80% of the population is older than 75 and 20% are younger than 75 would be assigned to the age ≥75 group (if their individual data cannot be separated from the study) when subgrouping for this factor.	
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	N/A
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	Acenocoumarol; Anticoagulation; Antiplatelet; Aspirin; Biological heart valve; Clopidogrel; Heart valve disease; Intervention; Phenindione; Prasugrel; Surgical valve repair; Surgical valve replacement; Ticagrelor; Transcatheter valve repair; Transcatheter valve replacement; Warfarin	
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	