External Assessment Group's Protocol

GID-HTE10027 Transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in people with aortic stenosis: late-stage assessment

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Abbreviations

Term	Definition
AKI	Acute kidney injury
BCIS	British Cardiovascular Intervention Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
DARS	Data Access Request Service
DataSAT	Data Suitability Assessment Tool
EAG	External Assessment Group
EuroSCORE	European System for Cardiac Operative Risk Evaluation Score
GIRFT	Getting It Right First Time
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPG	Interventional Procedures Guidance
MCDA	Multi-criteria decision analysis
NMA	Network meta-analysis
NMB	Net monetary benefit
NACSA	National Adult Cardiac Surgery Audit
NICOR	National Institute for Cardiovascular Outcomes Research
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
TAVI	Transcatheter aortic valve implantation
RCT	Randomised controlled trial
SAVR	Surgical aortic valve replacement
STS	The Society of Thoracic Surgeons

1 Background and objectives

1.1 Background

Transcatheter aortic valve implantation (TAVI) is a procedure that involves replacing the aortic heart valve using a narrow flexible tube (catheter) inserted through a blood vessel in the leg or chest. The procedure is carried out under general anaesthesia or under local anaesthesia with or without sedation. The procedure is used to treat patients with impaired outflow of blood from the heart (aortic stenosis), which is a condition that can lead to heart failure and death. Aortic stenosis is often treated with cardiac surgery, which involves the need for sternotomy and cardiopulmonary bypass; TAVI aims to provide a less invasive treatment option. The procedure requires delivery and loading systems for implantation of the valve, therefore the EAG will use the term 'TAVI devices' to encompass the valve and implantation systems and 'TAVI' when referring to the procedure.

TAVI is currently conducted in 42 NHS centres in England and can be an elective or emergency procedure, with 72.9% of procedures being elective between 2022 and 2023 (National Institute for Cardiovascular Outcomes Research [NICOR], 2024). The 2021 Getting it Right First Time (GIRFT) National Cardiology Report considered several optimisation measures for aortic valve disease services in the NHS, including increased use of local anaesthesia with sedation, use of a transfemoral access approach, refinements in the delivery equipment, same day discharge where appropriate, and having a single point of contact to co-ordinate patient care. Pre-operative assessment for TAVI may also be conducted more locally for the patient, rather than within specialist cardiology services.

As of 22 January 2024, there are 11 TAVI devices from 8 manufacturers available through NHS Supply Chain; all contain material derived from animal sources (bovine or porcine) and a nickel alloy valve frame.

1.2 Objectives

The objective of this assessment is to assess the incremental clinical, economic, and non-clinical benefits of TAVI devices for people with aortic stenosis to determine whether price variation is justified and inform procurement decisions. The EAG will assess the incremental clinical and economic benefits of TAVI devices, while NICE will assess the user preferences through a separate process using multi-criteria decision analysis (MCDA) principles.

2 Decision problem

NICE, together with several experts in TAVI and NHS cardiology pathways, patient representatives, and other stakeholders, developed a Final Scope for the assessment of TAVI devices.

2.1 Population and subgroups

The target population for this assessment is adults with symptomatic severe aortic stenosis who are eligible for TAVI. Several subgroups have been considered within the Final Scope. The EAG will consider additional subgroups where feasible and as considered appropriate by the Clinical Experts.

NICE updated their Interventional Procedures Guidance (IPG) for TAVI in 2017 (IPG586), which considered evidence in 3 subgroups of patients with aortic stenosis based on suitability of surgical aortic valve replacement (SAVR):

- For whom SAVR is considered unsuitable.
- For whom SAVR is considered suitable but poses a high risk.
- For whom SAVR is considered suitable and for whom it does not pose a high risk.

While TAVI was determined to be clinically effective in all surgical risk groups, section 1.5.3 of the NICE Guideline NG208 concluded that “TAVI is not cost-effective for people at low or intermediate surgical risk at the current list price”. In January 2023 (updated May 2023), NHS England (NHSE) published a

commissioning policy position statement broadening access to TAVI for eligible patients with intermediate or low SAVR risk to alleviate pressures on local systems in supporting elective performance.

Recommendations 1.2 of IPG586 and IPG653 note that details of all TAVI procedures should be entered into the UK TAVI Registry; data entry to this Registry is mandated (Ali et al. 2023). The EAG consider that the UK TAVI Registry is the most robust data source that is generalisable of practice and outcomes of TAVI procedures conducted in a UK NHS setting. The EAG note that the UK TAVI Registry does not currently record surgical risk group, and this cannot be robustly calculated retrospectively due to missing fields and data completeness of existing data fields. Therefore, the EAG acknowledge that data from the UK TAVI Registry will represent a mixed patient risk group. The EAG further notes that the quality of reporting surgical risk in the published literature is variable; with incomplete reporting, use of clinical judgement, and use of different scoring systems (STS, logistic EuroSCORE I and EuroSCORE II). Clinical Experts also advised that interventional cardiologists do not routinely score surgical risk in TAVI patients, and therefore the EAG would consider that surgical risk cannot guide selection of which TAVI device to use (in line with the decision problem) limiting its value in subgroup analysis. However, the EAG will liaise with Clinical Experts to determine patient characteristics that do routinely guide the selection of which TAVI device to use, that could be used in appropriate subgroup analysis.

The EAG acknowledge that some TAVI devices are selected based on specific clinical indications or considerations (Ali and Blackman, 2019), therefore the EAG will consult with the Clinical Experts to determine population characteristics that influence the decision-making process for which device to use (for example, where only 1 available device may be appropriate for use). The EAG will liaise with Clinical Experts to define specific patient subgroups where only certain devices in Scope may be used, to enable meaningful subgroup comparisons or scenario analyses.

NICE have considered TAVI as a less invasive treatment option where a previous aortic bioprosthetic valve has failed in IPG653, known as valve-in-

valve TAVI. While the proportion of patients undergoing a secondary aortic valve intervention using a TAVI device is small (between 3% and 5% of TAVI procedures annually between 2013 to 2023 were for aortic bioprosthetic valve failure, NICOR Annual TAVI Report, 2024). The Clinical Experts advised that the expansion of TAVI use in low and intermediate surgical risk groups (and generally younger patients) will likely result in an increase in this proportion in future. The EAG note that not all technologies included within this assessment are explicitly indicated for TAVI within a prior bioprosthetic aortic valve. The EAG will consider evidence for in-valve TAVI for all devices where this is not explicitly contraindicated according to the device Instructions for Use.

2.2 Intervention

On 22 December 2023, the EAG contacted NHS Supply Chain to confirm the list of TAVI devices currently available to the NHS, and the subset that were newly added to the NHS Supply Chain framework from September 2023 (indicating devices which are likely to have limited UK evidence). NHS Supply Chain confirmed that 11 devices were available on 22 January 2024. This included 3 balloon-expanding devices:

- Myval Octacor (Meril)
- Sapien 3, Sapien 3 Ultra (Edwards Lifesciences)

As well as 8 self-expanding devices:

- ACURATE Neo2 (Boston Scientific)
- Allegra (Biosensors)
- Evolut R, Evolut Pro+, Evolut FX (Medtronic)
- Hydra (SMT)
- Navitor (Abbott)
- Trilogy (JenaValve)

NHS Supply Chain also noted that Evolut FX was added in December 2023 to a limited number of NHS Trusts and was anticipated to be available to all NHS Trusts from March 2024. Furthermore, NHS Supply Chain confirmed that Evolut Pro (Medtronic) remains available for purchase, however the Company

have stated that the device is no longer commercially available, therefore it has not been included within the Final Scope published 11 December 2023. The EAG will summarise the innovative features of each TAVI device as reported by the Company in their completed Request for Information form submitted to NICE.

The EAG will tabulate key elements of the indications for use for each device, and will consider the surgical risk group and suitability for in-valve replacement (as stated in the manufacturer instruction for use) in the EAG Report. The EAG note that differing indications for use across TAVI devices should be considered when interpreting results from real-world evidence, as some TAVI devices may include a more heterogenous case mix of patients, whilst for other devices the treated population is comparatively homogeneous.

2.3 Potential alternative technologies

Where generalisable evidence for the device model in the Final Scope is lacking, the EAG will consider evidence related to an earlier generation of the technology, in line with the Interim Methods and Process Statement for Late-Stage Assessment (NICE, 2024). The EAG note that this approach has limitations because of existing evidence suggesting differences in outcomes between TAVI device generations. For example, the meta-analyses by Abdelfattah et al. (2022) and Elgendy et al. (2020) found that post-operative paravalvular leak, which can lead to reintervention, occurs significantly less frequently with newer generation Edwards Lifesciences and Medtronic TAVI devices compared with their predecessors. The systematic review and cost-effectiveness report by Heathcote et al. (2023) reported from a multivariate analysis that device generation was independently associated with the probability of TAVI being cost-effective when compared with SAVR.

The EAG will tabulate technological differences between device generations, and any anticipated newer iterations expected in the next 12 months as described by the Companies within the EAG Report.

2.4 Comparators

Current NICE guidance (NG208 published in 2021, and IPG586 updated in 2017) recommends TAVI as first-line treatment in patients at high surgical risk or where SAVR is considered unsuitable. As a result, the latest data from the National Adult Cardiac Surgery Audit (NACSA) suggest that only 2.7% of SAVR procedures are done in a high surgical risk population with most patients (89.0%) receiving SAVR being considered a low surgical risk (NACSA, 2024). The EAG also note that the number of patients receiving TAVI compared with SAVR has increased, with 7,695 and 3,623 receiving each treatment respectively between 2022 and 2023. There is also an increasing TAVI to SAVR ratio with 2.1 TAVIs per SAVR procedures between 2022 and 2023 (NACSA, 2024), up from 0.3 TAVIs per SAVR procedure between 2016 to 2017. As uptake of TAVI has increased, the mortality rate of high surgical risk patients receiving isolated SAVR has dropped from over 9% between 2020 and 2021 to 3.1% between 2022 and 2023 (NACSA, 2024). Whilst the EAG acknowledge SAVR as an appropriate comparator for patients deemed of low or intermediate surgical risk, SAVR was excluded as a comparator in the context of this late-stage assessment for the following reasons:

- The decision problem focuses on incremental differences between TAVI devices.
- Clinical Experts advised that clinical practice has remained largely consistent following the NHSE position statement (with the majority of TAVI cases being surgical high risk).
- Not all TAVI devices are indicated for use in low or intermediate surgical risk, but the definition of these risk groups varies by manufacturer, and surgical risk is not captured and cannot be derived from the UK TAVI Registry to enable differentiation in analyses.

Therefore, the EAG have focused on the choice of TAVI device used when the clinical decision has been made that TAVI is the most appropriate treatment option. This late-stage assessment does not address the cost-effectiveness of TAVI compared with SAVR or the clinical factors that

influence the decision to offer TAVI, SAVR, or no intervention, which was covered within NG208. Complicating this however is that, the choice of TAVI device is based on clinical characteristics; for example, the 2020 ACC/AHA Guideline for the management of patients with valvular heart disease (Otto et al. 2021) states that "the specific choice of a balloon-expandable valve or self-expanding valve depends on patient anatomy and other considerations". The Clinical Experts consulted as part of this late-stage assessment have advised that a range of factors are considered when selecting an appropriate TAVI device, including risk of reintervention, risk of pacemaker implantation, and calcification, which is further supported by published evidence (Ali and Blackman, 2019). The EAG therefore have focused on the decision problem that a choice has been made to use TAVI and it is the type of TAVI device that is being assessed. Consequently, the EAG have not considered SAVR as a comparator either directly in primary studies or as a node in network meta-analyses. It is the EAG's view that inclusion of SAVR would potentially compromise the transitivity assumption of network meta-analyses as this leads to risk of confounding by indication that cannot be accounted for.

2.5 Outcomes

Outcomes (and timepoints considered) that were incorporated within the economic model used during NG208 included.

- Mortality (in-hospital and longitudinally to 15 years).
- Length of hospital stay, including intensive care unit (ICU) stay (in-hospital).
- Reintervention rate (longitudinally to 15 years).
- Stroke (in-hospital).
- Vascular complications (in-hospital).
- Acute kidney injury (AKI and need for dialysis; in-hospital).
- Pacemaker implantation (in-hospital).
- Paravalvular leak (in-hospital).
- Conversion to surgery (in-hospital).

- Bleeding (in-hospital; additional outcome not listed within NICE Final Scope).
- Health-related quality of life (longitudinally to 15 years; age and sex-based utilities are captured within the model, and disutilities captured from adverse events such as stroke, major bleeding, vascular complication, and dialysis occurring post-procedure).

Additional outcomes, and outcomes at additional timepoints may be considered by the EAG where appropriate, for example where a difference between TAVI devices is identified from the data sources that may impact the costs and quality-adjusted life years (QALYs). The EAG will consult with Clinical Experts to ensure changes to clinical inputs are appropriate.

User preference (which was considered as a significant contributory factor in the GIRFT, Cardiology report, 2021), and outcomes not considered within the EAG modelling may be addressed independently by NICE as part of the MCDA process (Interim Methods and Process Statement for Late-Stage Assessment; NICE 2024).

2.6 Other considerations

Equality considerations were described in IPG586 and NG208 and within the supporting equality impact assessment documents. Further equality considerations have been considered by NICE in the Equality Impact Assessment (2024) for this late-stage assessment.

The EAG note that some patients may not accept or may have preferences for specific TAVI devices on religious or cultural beliefs because of the use of animal-derived products, either bovine or porcine, across the available TAVI devices (Easterbrook and Madden, 2008; Eriksson et al. 2013). Furthermore, differences in long-term clinical (mortality, reoperation, infective endocarditis) and structural durability outcomes between porcine and bovine valves used in SAVR have been reported (Persson et al. 2021; Jung et al. 2023; Glaser et al. 2024). Therefore, the EAG will conduct exploratory analyses of TAVI devices within pericardial tissue material types.

Furthermore, all TAVI devices included within this assessment contain nickel and so are contraindicated in patients with a nickel allergy or sensitivity; allergy to nickel disproportionately affects females (Ahlström et al. 2019; Schuttelaar et al. 2018). The EAG will request information from each Company regarding nickel-related adverse events and will summarise responses within the EAG report to determine whether this should be incorporated as an outcome within the economic evaluation.

Aortic heart valves typically have 3 leaflets, known as a tricuspid aortic valve. A bicuspid valve, where an aortic heart valve has 2 leaflets, is the most common congenital heart defect, occurring in between 1% to 2% of the general population (Verma et al. 2023), affecting twice as many males as females (Mubarik et al. 2023). Furthermore, unicuspid valves, where an aortic valve has a single leaflet, is a rare congenital anomaly that disproportionately affects males (Singh et al. 2015) and is considered to affect 0.02% of the adult population undergoing an echocardiogram (Novaro et al. 2003) and 5% of patients undergoing surgery for aortic stenosis (Roberts and Ko, 2005). The EAG will tabulate and summarise the indications for use which specify valve morphology for the TAVI devices in Scope of this late-stage assessment. The EAG note that leaflet configuration is not captured within the UK TAVI Registry, and therefore will not be incorporated into analyses or economic modelling, which is a limitation of this late-stage assessment. As non-tricuspid morphology represents a small proportion of patients, the impact of this is limited.

Religion or belief and sex are protected characteristics under the Equality Act 2010.

The EAG will liaise with Clinical Experts to consider whether any additional equality considerations exist, or whether there is considered inequality across TAVI devices.

3 Evidence synthesis

3.1 Search methods

Economic evidence

The EAG conducted scoping searches for economic evaluations of TAVI which were published after NG208 (Appendix A). The EAG will use these publications alongside analysis of the UK TAVI Registry and HES to inform structure and parameter updates of the economic model that was used within NG208.

Clinical evidence

Early scoping literature searches by the EAG have not identified any systematic review or meta-analysis directly relevant to the decision problem (Appendix A). However, the EAG will consider the relevance of systematic reviews to address uncertainties relating to TAVI devices or manufacturers where UK TAVI Registry or HES data is lacking. The original economic model developed for NG208 incorporated both real-world evidence (focusing on adverse events) and randomised controlled trial (RCT) evidence (focusing on relative effects between TAVI and SAVR) to evaluate the cost-effectiveness of TAVI compared with SAVR. However, multiple consultation comments were received during the NG208 guideline development that raised concerns that trial participants of the included RCTs were not representative of a UK NHS population (NG208 Consultation Comments and Responses, 2021) and hence may not be relevant to the NHS.

Network meta analyses (NMA) could be used to estimate relative effects of devices, based on published RCTs, but NMA has limited applicability to the decision problem because the assumption of transitivity is questionable (transitivity requires that each patient *could* have been randomised to all devices). The Clinical Experts have previously advised that patient characteristics (anatomical and clinical risk factors) inform the choice between expansion type and can be a strong predictor of clinical outcome (Bradley et al. 2019). This is supported by clinical guidance (Otto et al. 2021) and

published evidence (Van Belle et al. 2020; Jose et al. 2015; Abdel-Wahab et al. 2014), with TAVI device expansion type leading to differences in cost effectiveness (Heathcote et al. 2023). Comparisons using real-world UK evidence are also limited because of possible confounding by indication. Both limitations arise because clinical experts have stated that their choice of TAVI partly depends on the characteristics of patients and valves. NMA has the added limitation, identified as a problem in NG208, of not being necessarily generalisable to UK.

Because the clinical outcome measures incorporated in the economic model focus on adverse events and mortality, and as the decision problem focus of this late-stage assessment is on the comparison of TAVI devices currently being used in the NHS, the EAG consider that observational and real-world data from the UK NHS are the most appropriate and reflective of actual current clinical practice. Large comprehensive cohorts are likely to provide more reliable data in such circumstances. RCT data is also unlikely to be comparable or extrapolated to real-world NHS evidence. For example, Abdel-Wahab et al. (2014) noted differences in aortic regurgitation between balloon- and self-expanding TAVI devices across the published non-randomised literature that is not seen in the RCT evidence. The reason for this is unclear but could be because of the atypical nature of patients and practitioners, that are not representative of real-world practice. Furthermore, the systematic review and meta-analysis by Swift et al. (2021) noted differences in mortality between TAVI and SAVR, which was not seen when only RCT evidence was considered. Otto et al. (2021) noted that RCT inclusion criteria, such as surgical risk or age, may restrict extrapolation of outcomes to real-world practice or other patient groups. The EAG will include discussion of limitations and generalisability of included evidence within the EAG report.

Long-term evidence (beyond 2 years) for TAVI was lacking within NG208. Therefore, the EAG will explore data linkage of the UK TAVI Registry to routine administrative data sources to determine long-term outcomes following TAVI (for example subsequent aortic valve implantation). This approach has limitations, for example patients with degenerated tissue valves

may not undergo reintervention because of frailty (Jabbour and Curzen, 2023), although they may be expected to have a higher mortality. Furthermore, most available long-term evidence is for older device generations (Ali et al. 2023) and outcomes have been noted to differ between generations. The Clinical Experts have previously advised that patient characteristics (anatomy and degree of calcification) inform the choice between expansion types and can be a strong predictor of clinical outcomes (Bradley et al. 2019). The EAG note that analyses comparing outcomes from different TAVI devices should adjust for confounders such as selection bias, procedural technique, and patient characteristics informing device selection (Bansal et al. 2023; Wang et al. 2023; Al-Abcha et al. 2021). The EAG also note that the major cost drivers in the economic model in NG208 included re-intervention rate and adverse events associated with the procedure.

The EAG note that the TAVI technologies available on NHS Supply Chain were updated on 18 September 2023 (see Section 2.2) where 4 of 8 manufacturers (Biosensors, Meril, SMT, Jenavalve) included in this assessment were added for the first time. Newer devices from manufacturers already included on NHS Supply Chain have also been added since September 2023. Therefore, the EAG acknowledge that not all technologies listed as interventions in the Final Scope may have sufficient data available to model each device separately using real-world data in an NHS setting.

Because of these considerations, the EAG will take a hierarchical approach to the evidence source when updating the clinical parameters in the economic model and exploring device clinical efficacy:

- The EAG considers the UK TAVI Registry (managed by NICOR, and mandated data entry) to be the most robust source of real-world data, which should include all TAVI procedures from every centre conducting the procedure across the UK, therefore ensuring generalisability. Age and sex of the population and adverse event outcomes from this national registry were used to inform the original NG208 economic model. However, the EAG notes that a limitation of the UK TAVI Registry is its focus on in-hospital outcomes and lack of longer-term

outcomes. A request for patient-level data from 01 April 2021 onwards was submitted to NICOR (22 December 2023) and data received (05 March 2024).

- The EAG will also identify a cohort of TAVI patients in England from the Hospital Episode Statistics (HES) database using clinical procedure codes (Rice et al. 2023) to derive aggregated TAVI population characteristics (such as age, sex), length of hospital and critical care stay, short-term complications (such as stroke, bleeding, pacemaker implantation) and long-term outcomes (such as aortic valve reintervention rate) and mortality, all of which are routinely coded. The EAG will use its existing pseudonymised data extracts from HES and the Civil Registration Mortality datasets. As HES lacks device (make and model) information, the EAG will perform data linkage between HES and the received UK TAVI Registry data as part of data validation and to obtain manufacturer or device-specific long-term outcomes (lacking from the Registry). To ensure that HES data is representative of the included devices in Scope, analysis of HES data will be restricted to data from 01 April 2021 onwards. Patient characteristics of those matched and unmatched will be compared to considered generalisability of results from the linked dataset.
- Where manufacturer- or device-specific data is unavailable in the UK TAVI Registry, the EAG will also consider publications, including those from other national TAVI registries, identified through targeted searches for peer-reviewed published evidence using the device name. The EAG will exclude animal studies, laboratory studies, non-research items and duplicate publications only. To supplement these searches, the EAG will request and consider published data from the Companies including longest-term evidence and comparative evidence compared with other TAVI devices in Scope of this assessment. Where reported, the EAG will explore differences in outcomes between device generations within the EAG Report.

3.2 Study selection

Studies will be considered in line with the hierarchy described in Section 3.1. When considering published evidence, priority will be given to large sample sizes, longest follow-up, comparative studies, and those conducted in a UK or UK NHS setting.

Because of the volume of published evidence for TAVI, the EAG will not consider additional non-published evidence supplied by Companies. The EAG will highlight any identified evidence gaps to advise future research, where appropriate. Publications identified in Scope but not prioritised for inclusion will be summarised in an appendix of the EAG Report. Excluded studies will be tabulated in the EAG Report with reasons for exclusion.

3.3 Data extraction strategy

The UK TAVI Registry patient-level data will be provided in a suitable file format by NICOR to the EAG (data processor), with NICE acting as the data controller. Data will be extracted and formatted using the data field specification (v4.09) available on the NICOR website. Data from HES are currently available to the EAG as pseudonymised data extracts supplied under the DARS agreement (DARS-NIC-170211-Z1B4J). Data will be extracted and formatted using the data specification available on the NHS Data Dictionary available on the NHS Digital website. All analysis will be completed using the statistical programming language R.

For evidence comparing clinical outcomes across multiple TAVI devices (regarded as 'key evidence' in the context of this late-stage assessment) the EAG will tabulate the study characteristics so that differences can be easily identified. This will include the following.

- Source information (such as author, year and trial registration where available).
- Study design (including recruitment dates, inclusion and exclusion criteria, setting including single- and multi-centre and country).

- Participant characteristics (inclusion and exclusion criteria, and general reporting of surgical risk group and valve morphology where reported).
- Intervention characteristics (such as TAVI device used, expansion type, access route, TAVI in native aortic valve or previous failed bioprosthetic valve [TAVI-in-TAVI, or TAVI-in-SAVR]).
- Patient outcomes (such as, aortic valve reintervention rates, health-related quality of life, adverse events [such as TAVI intraoperative conversion to SAVR, pacemaker implantation, vascular complication, stroke, major bleeding, dialysis, paravalvular leak and severity, mortality, length of hospital or ICU stay] as incorporated in the NG208 economic model), including duration of follow-up.

Data extraction will be conducted by 1 reviewer and will be quality assessed by a second reviewer.

3.4 Quality assessment strategy

The economic model developed as part of NG208 will be critically appraised using the CHEERS Checklist (2022), (Husereau et al. 2022). The EAG will not conduct critical appraisal of any sources used to inform the original NG208 economic model because it is assumed this was done as part of NG208. Where updated primary clinical evidence is used to inform the economic evaluation within this assessment, the EAG will use an appropriate critical appraisal tool relevant to the study design. The Data Suitability Assessment Tool (DataSAT) will be used to assess the suitability and quality of the Registry and HES data used to inform the economic evaluation (NICE ECD9, 2023). For devices lacking real-world evidence in the UK, where there remains uncertainty regarding its comparative performance against other TAVI devices in scope preventing its incorporation in the economic evaluation, the EAG will summarise the highest-level evidence associated with that device and will summarise the key strengths, limitations and comment on the generalisability of the results to clinical practice in the NHS.

3.5 Methods of analysis/synthesis

To determine whether there is a significant change in case mix over time (see Section 2.1), the EAG will consider whether patient demographics that contribute to a surgical risk score (European System for Cardiac Operative Risk Evaluation Score [EuroSCORE] II; noting that not all data fields are available in the Registry to calculate the EuroSCORE II directly) differ significantly between 2021 to 2022 and 2022 to 2023 financial years.

The EAG will apply several steps prior to analysis of UK TAVI Registry data, including cleaning (for example removing erroneous data based on conflicting data between valve manufacturer and model, unconfirmed valve deployment, deviation from the published data field specification (v4.09), or duplicated entries), formatting, and reporting of data completeness of each data field. The EAG will ask each Company to confirm device models for serial numbers recorded in the Registry. As some covariates are potentially associated (for example: sex, height, valve diameter, valve area, valve size), multiple imputation will not be used to correct for missing data for each variable in isolation. To assess the effect of missingness, where possible, for each analysis, outcome measures will be compared univariately between rows with all explanatory variables present and rows where one or more are missing. Data items will be calculated where needed, for example, length of stay from dates of admission and discharge. The EAG will liaise with the UK TAVI Registry Clinical Lead to determine which variables captured within the UK TAVI Registry should be considered as patient demographic descriptors, confounders, and outcomes within subsequent analysis. Appropriate univariate and multivariate analysis will be used to explore the relationship between data items in the Registry for each TAVI device or manufacturer. In univariate analyses, Bonferroni-Holm correction will be applied to adjust the significance level (p=0.05) to account for multiple hypothesis testing. Multivariate analyses will be conducted using covariates identified through discussions with the Clinical Lead of the UK TAVI Registry. Expert opinion will be sought to confirm clinical significance of all results. Outcomes that significantly differ between devices, will be considered in structural changes to the economic model. Subgroup analysis will be considered (for example,

where balloon- or self-expanding devices may be used) as described in Section 2.1, taking confounders into account as needed.

The same steps in processing patient-level data from HES will be applied as when processing patient-level data from the UK TAVI Registry (that is data cleaning, formatting, reporting of data completeness, univariate and sensitivity analyses). Additional outcomes post-discharge will be captured in HES, which are not routinely collected in the UK TAVI Registry (which lacks follow-up data), including need for subsequent aortic valve procedure (determined through procedure codes), stroke (determined through diagnosis codes) and mortality (from HES linked to Office for National Statistics, including cause of death). Kaplan-Meier analysis will be undertaken to report longer-term outcomes at 30 days, 1 year and 2 years accounting for variable patient follow-up (including number of events and number at risk at these timepoints), which could be extrapolated for use in long term economic modelling. Expert opinion will be sought to confirm clinical significance of results. As a validation check, the UK TAVI Registry data will be compared with published BCIS or NICOR annual reports for TAVI.

Pseudonymised data linkage between the HES and UK TAVI Registry datasets will use the NHS Trust, dates of procedure, admission, and discharge, patient sex, age, and comorbidities. This will enable identification of device-specific or manufacturer-specific (where specific device data is lacking) long-term outcomes. Demographics of the matched Registry cohort will be compared with the unmatched Registry cohort to determine whether they are a representative sample and to identify potential sources of bias. As part of validation checks, in-hospital outcomes available in both UK TAVI Registry and HES datasets will be compared. Multivariate analysis will be conducted in the matched cohort for longer-term outcomes. Additional exploratory analysis will be conducted using in-hospital outcomes as covariates (that is surrogacy analyses) to determine whether they are significant contributors to outcome, which may inform structural changes to the economic model.

Values from real-world data sources (for example mean and standard deviation, or numerator and denominator, as appropriate to the type of variable) will be used within the probabilistic sensitivity analysis of the economic modelling to consider the uncertainty associated with each included variable, Section 4.3. A narrative summary of the key evidence identified for each manufacturer in Scope of this late-stage assessment will be included within the EAG Report, including areas of uncertainty.

4 Economic evaluation

As per the Final Scope, the economic evaluation will be developed from the health economic model used for the NICE guidance (NG208), and will focus on 3 main areas.

- To evaluate and, if necessary, update the economic model developed for NG208 to represent current practice, based on national guidance and policy, real-world experience, and recent data.
- To assess the value for money of individual TAVI devices, based on the costs and effects.
- To identify the key cost drivers and uncertainties of the economic evaluation.

4.1 Model update

The EAG will further develop the health economic model used for the NICE guidance (NG208) to include functionality to comparison of TAVI devices (instead of only two, as in the original economic model for NG208). To do this, the EAG will rebuild the economic model in R programming language using the *rdecision* package. The EAG will amend the existing economic model used for NG208 to incorporate outcomes captured routinely in the NHS UK real-world evidence sources (UK TAVI Registry and Hospital Episode Statistics) where significant differences between devices have been identified. Amendments to the economic model developed for NG208 to address the decision problem in this late-stage assessment will be summarised within the EAG Report. The EAG will compare the overall economic model structure with those used in economic evaluations of TAVI published after NG208 and will

liaise with Clinical Experts to consider additional structural changes to the economic model to reflect current NHS care, or to better address the decision problem (such as, to evaluate the incremental differences between multiple TAVI devices).

Utility and disutility values used in the economic model will be reviewed and compared with values used in economic evaluations of TAVI published after NG208 guidance. Justification for a new or updated source selection will be clearly documented within the EAG Report. Where multiple values are considered appropriate, sensitivity analysis will be conducted.

Within the NG208 economic model, incorporated costs include intervention costs (relating to the procedure via Healthcare Resource Group [HRG] codes and TAVI device, which is reimbursed separately under the NHSE Specialised Services Devices Programme, formerly known as the High-Cost Tariff-Excluded Devices programme), cost of adverse events, aortic valve reintervention, hospitalisation and rehabilitation. The EAG will conduct a top-down costing approach to the TAVI HRG to enable in-hospital outcomes to vary between TAVI devices. The proportion of patients experiencing an in-hospital event, and aggregated length of hospital stay will be based on aggregated outcomes from HES. The cost of ICU stay will be considered in addition to the TAVI HRG (as this is not included within the core HRG bundle). Costs of TAVI devices will be obtained directly from NHS Supply Chain. Remaining costs obtained from NHS Reference costs will be updated to 2021 to 2022 (NHS England, 2023). Costs will be expressed in UK pound Sterling (2022), and where updated costs are not available, costs will be inflated to the price year 2022. In line with the NICE reference case (PMG36), both costs and outcomes will be discounted at 3.5% annual discount rate, and the perspective of analysis will be that of the UK NHS and personal social services. In the base case scenario, a time-horizon reflecting the longest available follow-up will be used; different time horizons explored within sensitivity analyses. For devices not captured in the UK TAVI Registry, data from key peer-reviewed publications will be considered as separate scenario analyses, but only where data is available and for timepoints reported. The

EAG considered that extrapolating immediate (in-hospital) or short-term (30-day) outcomes to longer term (1 year or more) was inappropriate for class III implantable devices where the long-term outcomes for the manufacturer were unknown. Particularly as several aortic valve devices have been withdrawn from market (for example, the Lotus Edge [Boston Scientific], Trifecta, Trifecta GT [Abbott]).

4.2 Individual TAVI device modelling

The EAG will use the clinical parameters from the UK TAVI Registry and HES to inform the economic modelling for each device or manufacturer, where data allows. The EAG will consider clinical endpoints in line with the Valve Academic Research Consortium-3 (VARC-3) standardized clinical endpoints for transcatheter and surgical aortic valve clinical trials. The EAG will select the most appropriate comparator for the base case, for example the most used device or manufacturer represented in the UK TAVI Registry dataset.

When a full cost-effectiveness analysis is needed and where possible, incremental cost-effectiveness ratios (ICERs) will be generated. The EAG will also consider the estimation of net monetary benefit (NMB) or incremental NMB where appropriate. The EAG will also report the probability of each device yielding the greatest NMB from PSA analyses.

Where UK TAVI Registry and HES data are not available for technologies in Scope, published comparative evidence for earlier versions of the technologies or between-devices for the manufacturers in Scope of this late-stage assessment will be considered where data permits, but restricted to the timepoints reported.

4.3 Sensitivity analysis

A range of sensitivity analyses (for example, by varying time horizons, cost of the TAVI device, cost of stroke and utilities) will be conducted to test the robustness of the model to changes in parameter assumptions and potentially to alternative data sources. To assess the overall uncertainty in the model

estimates, both deterministic and probabilistic sensitivity analyses will be conducted.

Secondary TAVI procedures

NICE IPG653, relating to valve-in-valve TAVI, Recommendation 2.2 notes that "reoperative surgery is associated with significant morbidity and a higher risk of mortality than primary surgery". Furthermore, Fovino et al. (2020) reported differences in subsequent coronary access post-TAVI compared with post-TAVI-in-TAVI. Because of differences in patient characteristics and surgical risks associated the EAG will consider outcomes of second-line TAVI procedures (either TAVI-in-SAVR, or TAVI-in-TAVI) separately to first-line TAVI procedures. The EAG will also consider reintervention using the same or different TAVI valve to determine the impact on results.

TAVI device expansion type (balloon versus self)

The Clinical Experts have previously advised that patient characteristics (anatomical and clinical risk factors) inform the choice between expansion type and can be a strong predictor of clinical outcome (Bradley et al. 2019). Because of differences in indication and outcomes between TAVI device expansion type (balloon or self), the EAG will compare clinical evidence of TAVI devices of the same expansion type.

Valve pericardial tissue material (bovine versus porcine)

There may be surgeon and patient preferences for choice of a specific TAVI device including those based on religious or cultural beliefs (Easterbrook and Madden 2008; Eriksson et al. 2013). Differences in clinical outcomes (including valve durability and adverse events) between bovine and porcine heart valves used in SAVR have been reported (Persson et al. 2021; Jung et al. 2023; Glaser et al. 2024), which may lead to differences in cost-effectiveness. The EAG will therefore conduct exploratory analysis to consider comparing costs and outcomes of bovine and porcine TAVI devices within expansion types, where data allows. The EAG note that there may be limited

data on which to draw firm conclusions and that this analysis is likely to be hypothesis-generating.

4.4 Threshold analysis

To support committee decision-making for this late-stage assessment, the EAG will conduct threshold analysis to explore the impact of adjustment of key economic model drivers on the incremental NMB, to determine possible consequences that could justify differences in price across the technologies. For example, the EAG may conduct threshold analysis to determine the maximum technology price at which a net incremental NMB gain is seen against a comparator.

4.5 Quality assurance

For the economic evaluation quality assessment, the EAG will formally critically appraise the economic model developed within NG208 using the consolidated health economic evaluation reporting standards (CHEERS 2022) checklist (Husereau et al. 2022). The EAG will also replicate the NG208 base case using the model when rebuilt in R programming language using the *rdecision* package.

The internal validity of the updated economic model will be checked independently by health economists within the EAG and will be undertaken by varying model input parameters and assessing whether the model results are sensitive and logical. Each model parameter will be checked against its source to ensure that it has been incorporated within the economic model appropriately. The updated model structure, assumptions, clinical parameters, and results from the updated model will be shared with Clinical Experts to ensure clinical validity.

5 Handling information

Technical and regulatory information received up to 31 May 2024 will be summarised in the EAG Report. Where information is not received from the manufacturers included within the late-stage assessment, the EAG will consider information available in the public domain.

Any ‘commercial in confidence’ data provided and specified as such will be highlighted in blue and underlined in the EAG Report. Any ‘academic in confidence’ data provided will be highlighted in yellow and underlined in the EAG Report. Any ‘personally identifiable’ data provided will be highlighted in pink and underlined in the EAG Report. Any ‘confidential price agreements’ data provided will be highlighted in green and underlined in the EAG Report.

6 Competing interests of authors

None.

7 Timetable/milestones

Milestone	Date to be completed
Deadline of Company submissions for inclusion in Late-Stage Assessment Report	31 May 2024
Submission of final protocol	05 June 2024
Submission of final Late-Stage Assessment Report	13 June 2024

8 References

Abdelfattah OM, Sayed A, Ghonim M, et al. (2022) Meta-analysis of transcatheter aortic valve implantation using the Sapien 3 versus Sapien 3 Ultra valves. Am J Cardiol. 168: 170-2

Abdel-Wahab M, Mehilli J, Frerker C, et al. (2014) Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA. 311(15): 1503-14

Ahlström MG, Thyssen JP, Wennervaldt M, et al. (2019) Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. Contact Dermatitis. 81(4): 227-41

Al-Abcha A, Saleh Y, Charles L, et al. (2021) Clinical outcomes of the self-expandable Evolut R valve versus the balloon-expandable Sapien 3 valve in transcatheter aortic valve implantation: a meta-analysis and systematic review. Cardiovasc Revasc Med. 25: 57-62

Ali N, Blackman DJ. (2019) TAVI: Which valve for which patient? Cardiac Interventions Today. 13(2): 72-78

Ali N, Hildick-Smith D, Parker J, et al. (2023) Long-term durability of self-expanding and balloon-expandable transcatheter aortic valve prostheses: UK TAVI registry. Catheter Cardiovasc Interv. 101(5): 932-42

Ayiku L, Levay P, Hudson T, et al. (2017) The MEDLINE UK filter: development and validation of a geographic search filter to retrieve research about the UK from OVID MEDLINE. Health Info Libr J. 34: 200-16

Azraai M, Gao L, Ajani AE. (2020) Cost-Effectiveness of Transcatheter Aortic Valve Intervention (TAVI) Compared to Surgical Aortic Valve Replacement (SAVR) in Low- to Intermediate-Surgical-Risk Patients. Cardiovasc Revasc Med. 21(9): 1164-8

Bansal A, Agarwal S, Braghieri L, et al. (2023) Subclinical leaflet thrombosis after balloon versus self-expandable transcatheter aortic valve implantation. Am J Cardiol. 192: 88-97

Bradley SM, Foag K, Monteagudo K, et al. (2019) Use of routinely captured echocardiographic data in the diagnosis of severe aortic stenosis. Heart. 105(2): 112-6

Cahill TJ, Raby J, Jewell PD, et al. (2022) Risk of infective endocarditis after surgical and transcatheter aortic valve replacement. Heart.108(8): 639-47

Canadian Agency for Drug and Technologies in Health (2016) Economic Evaluations and Models – MEDLINE [online; accessed 26 January 2024]

Canadian Agency for Drug and Technologies in Health (2021) SR/MA/HTA/ITC – MEDLINE, Embase, PsychInfo [online; accessed 26 January 2024]

Canadian Agency for Drug and Technologies in Health (2023) RCT / CCT - MEDLINE, Embase. [online; accessed 26 January 2024]

Chatfield A, Sathananthan J, Wood DA, Webb JG (2021) Next-generation balloon-expandable transcatheter heart valve: the SAPIEN 3 Ultra valve. Future Cardiol. 17(5): 811-6

Chotnoppharatphatthara P, Yoodee V, Taesotikul S, et al. (2023) Transcatheter aortic valve implantation in patients with severe symptomatic aortic valve stenosis: systematic review of cost-effectiveness analysis. Eur J Health Econ. 24(3): 359-76

Easterbrook C, Maddern G. (2008) Porcine and bovine surgical products: Jewish, Muslim, and Hindu perspectives. Arch Surg. 143(4): 366-70

Edlinger C, Krizanic F, Butter C, et al. (2021) Economic assessment of traditional surgical valve replacement versus use of transfemoral intervention in degenerative aortic stenosis. Minerva Med. 112(3): 372-83

Elgendy IY, Gad MM, Mahmoud AN, et al. (2020) Meta-analysis comparing outcomes of self-expanding versus balloon-expandable valves for transcatheter aortic valve implantation. Am J Cardiol. 128: 202-9

Eriksson A, Burcharth J, Rosenberg J. (2013) Animal derived products may conflict with religious patients' beliefs. BMC Med Ethics. 14: 48

Fovino LN, Scotti A, Massussi M, et al. (2020) Coronary angiography after transcatheter aortic valve replacement (TAVR) to evaluate the risk of coronary access impairment after TAVR-in-TAVR. J Am Heart Assoc. 9(13): e016446

Gilard M, Eltchaninoff H, Iung B, et al. (2022) Cost-Effectiveness Analysis of SAPIEN 3 Transcatheter Aortic Valve Implantation Procedure Compared With Surgery in Patients With Severe Aortic Stenosis at Low Risk of Surgical Mortality in France. Value Health. 25(4): 605-13

Glaser N, Sartipy U, Dismorr M. (2024) Prosthetic valve endocarditis after aortic valve replacement with bovine versus porcine bioprosthesis. J Am Heart Assoc. 13(1): e031387

Haute Autorité de Santé, HAS. (2021a) SAPIEN 3 MODEL 9600 TFX AORTIC VALVE BIOPROSTHESIS WITH EDWARDS COMMANDER™ PLACEMENT SYSTEM. Saint-Denis La Plaine [online; accessed 26 January 2024]

Haute Autorité de Santé, HAS. (2021b) COREVALVE EVOLUT PRO. Saint-Denis La Plaine [online; accessed 26 January 2024]

Health Technology Wales. (2020) Transcatheter Aortic Valve implantation to treat people with severe symptomatic aortic stenosis, who are at intermediate surgical risk. Evidence Appraisal Report [online; accessed 26 January 2024]

Heathcote L, Srivastava T, Sarmah A, et al. (2023) A systematic review and statistical analysis of factors influencing the cost-effectiveness of transcatheter aortic valve implantation for symptomatic severe aortic stenosis. Clinicoecon Outcomes Res. 15: 459-75

Hilling-Smith R, Smethurst J, Cockburn J, et al. (2021) Pre-procedural pacing bias among transcatheter aortic valves with higher post-procedure pacing rates: evidence from the UK TAVI Registry. Heart and Vessels. 36: 408-13

Himmels JPW, Flottorp S, Stoinska-Schneider A, et al. (2021) Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups: a health technology as-sessment. Oslo: Norwegian Institute of Public Health [online; accessed 26 January 2024]

Husereau D, Drummond M, Augustovski F, et al. (2022) Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated reporting guidance for health economic evaluations. Value Health. 25(1): 3-9

Inoue S, Nakao K, Hanyu M, et al. (2020) Cost-Effectiveness of Transcatheter Aortic Valve Implantation Using a Balloon-Expandable Valve in Japan: Experience From the Japanese Pilot Health Technology Assessment. Value Health Reg Issues. 21: 82-90

Jabbour RJ, Curzen N. (2023) How long will my TAVI valve last, doctor? Expert Rev Cardiovasc Ther. 21:11, 721-4

Jose K, Richardt G, Abdel-Wahab M. (2015) Balloon- of self-expandable TAVI: clinical equipoise? Interv Cardiol. 10(2): 103-8

Jung YJ, Choi JW, Kang Y, et al. (2023) Long-term results of a stented bioprosthetic valve in the aortic position: structural valve deterioration and valve haemodynamic deterioration of bovine pericardial and porcine valves. Eur J Cardio-thoracic Surg. 63(2): ezac506

Kalogeras K, Ruparelia N, Kabir T, et al. (2020) Comparison of the self-expanding Evolut-PRO transcatheter aortic valve to its predecessor Evolut-R in the real world multicentre ATLAS registry. Int J Cardiol. 310: 120-5

Krasopoulos G, Falconieri F, Benedetto U, et al. (2016) European real world trans-catheter aortic valve implantation: systematic review and meta-analysis of European national registries. J Cardiothorac Surg. 11(1): 159

Kuntjoro I, Tay E, Hon J, et al. (2020) Cost-Effectiveness of Transcatheter Aortic Valve Implantation in Intermediate and Low Risk Severe Aortic Stenosis Patients in Singapore. Ann Acad Med Singap. 49(7): 423-33

Latimer, N. NICE DSU Technical Support Document 14 (2013): Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. [online, accessed 26 January 2024]

Lee G, Chikwe J, Milojevic M, et al. (2023) ESC/EACTS vs. ACC/AHA guidelines for the management of severe aortic stenosis. Eur Heart J. 44(10): 796-812

Lorenzoni V, Barbieri G, Saia F, et al. (2021) The cost-effectiveness of transcatheter aortic valve implantation: exploring the Italian National Health System perspective and different patient risk groups. Eur J Health Econ. 22(9): 1349-63

Ludman PF. (2012) The UK transcatheter aortic valve implantation registry; one of the suite of registries hosted by the National Institute for Cardiovascular Outcomes Research (NICOR). Heart. 98(24): 1789-9

Myat A, Papachristofi O, Trivedi U, et al. (2020) Transcatheter aortic valve implantation via surgical subclavian versus direct aortic access: A United Kingdom analysis. Int J Cardiol. 308: 67-72

Myat A, Buckner L, Mouy F, et al. (2021a) In-hospital stroke after transcatheter aortic valve implantation: A UK observational cohort analysis. Catheter Cardiovasc Interv. 97: E552-9

Myat A, Mouy F, Buckner L, et al. (2021b) Survival relative to pacemaker status after transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 98: E444-52

NHS England. Position statement: Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR) for symptomatic, severe aortic stenosis (adults) to support elective performance [online; accessed 26 January 2024]

Otto CM, Nishimura RA, Bonow RO, et al. (2021) 2020 American College of Cardiology and American Heart Association Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol. 77(4): e25-197

Persson M, Glaser N, Franco-Cereceda A, et al. (2021) Porcine vs bovine bioprosthetic aortic valves: long-term clinical results. Ann Thorac Surg. 111(2): 529-35

Pinar E, García de Lara J, Hurtado J, et al. (2022) Cost-effectiveness analysis of the SAPIEN 3 transcatheter aortic valve implant in patients with symptomatic severe aortic stenosis. Rev Esp Cardiol (Engl Ed). 75(4): 325-33

Rice CT, Barnett D, O'Connell SP, et al. (2023) Impact of gender, ethnicity and social deprivation on access to surgical or transcatheter aortic valve replacement in aortic stenosis: a retrospective database study in England. Open Heart. 10: e002373

Ruggeri M, Donatella M, Federica C, et al. (2022) The transcatheter aortic valve implantation: an assessment of the generalizability of the economic evidences following a systematic review. Int J Technol Assess Health Care. 38(1): e27

Schuttelaar MLA, Ofenloch RF, Bruze M, et al. (2018) Prevalence of contact allergy to metals in the European general population with a focus on nickel and piercings: The EDEN Fragrance Study. Contact Dermatitis. 79(1): 1-9

Scotti A, Pagnesi M, Kim W-K, et al. (2022) Haemodynamic performance and clinical outcomes of transcatheter aortic valve replacement with the self-expanding ACURATE neo2. EuroIntervention. 18(10): 804-11

Swift SL, Puehler T, Misso K, et al. (2021) Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review and meta-analysis. BMJ Open. 11(12): e054222

Tam DY, Azizi PM, Fremes SE, et al. (2021a) The cost-effectiveness of transcatheter aortic valve replacement in low surgical risk patients with severe aortic stenosis. Eur Heart J Qual Care Clin Outcomes. 7(6): 556-63

Tam DY, Miranda RN, Elbatarny M, Wijeysundera HC. (2021b) Real-World Health-Economic Considerations Around Aortic-Valve Replacement in a Publicly Funded Health System. Can J Cardiol. 37(7): 992-1003

Van Belle E, Vincent F, Labreuche J, et al. (2020) Balloon-expandable versus self-expanding transcatheter aortic valve replacement: a propensity-matched comparison from the FRANCE-TAVI Registry. Circulation. 141(4): 243-59

Wang B, Mei Z, Ge X, et al. (2023) Comparison of outcomes of self-expanding versus balloon-expandable valves for transcatheter aortic valve replacement: a meta-analysis of randomized and propensity-matched studies. BMC Cardiovasc Disord. 23(1): 382

Zaid S, Attizzani GF, Krishnamoorthy P, et al. (2023) First-in-human multicentre experience of the newest generation supra-annular self-expanding Evolut FX TAVR system. JACC Cardiovasc Interv. 16(13): 1626-35

Zhou JY, Liew D, Duffy SJ, Walton A, Htun N, Stub D. (2021) Cost-Effectiveness of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients With Severe Aortic Stenosis. Heart Lung Circ. 30(4): 547-54

Appendices

Appendix A: Scoping literature searches

At the start of this project, to rapidly gauge the volume of literature published since the searches run for the existing NICE guideline (NG208), the existing MEDLINE search strategy used for Evidence Review H in NG208 was run aimed at including all technologies within the NICE draft Scope. The scoping searches were designed to identify both systematic reviews of clinical effectiveness and systematic reviews of economic evaluations and economic models. Search filters to identify systematic reviews of clinical effectiveness and systematic reviews of economic evaluations and models were applied. The search was limited by date from 01 January 2020 to the most recently available date in the relevant database to update the search and capture additional records added to the relevant database since the searches for NG208 in October 2020. This search identified 764 titles and abstracts, which were screened by a single reviewer for relevance to the decision problem. No publication directly addressed the decision problem or objectives of this assessment.

The search strategy, run only in MEDLINE ALL, is presented below.

Database:
Ovid MEDLINE(R) ALL <1946 to November 28, 2023>

Date searched: 29 November 2023

#	Query	Results from 29 Nov 2023
1	exp Heart Valve Diseases/	137,939
2	Heart Diseases/	74,953
3	exp Aortic Valve Stenosis/	52,160
4	Aortic Valve/	40,391
5	severe aortic stenosis.ab,ti,kw.	6,131
6	((primary or secondary) adj valv* disease*).ab,ti,kw.	53
7	((mitral valv* or aortic valv* or tricuspid valv* or pulmon* valv*) adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	11,114

#	Query	Results from 29 Nov 2023
8	((mitral leaflet* or aortic leaflet*) adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	5
9	(aortic valv* adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	5,177
10	(aortic leaflet* adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	1
11	((heart or cardiac) adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	431,280
12	((mitral or aortic or tricuspid or pulmon*) adj3 (prolaps* or regurgitation or stenosis or atresia or insufficien*)).ti,ab.	91,428
13	or/1-12	631,607
14	Heart Valve Prosthesis/	40,602
15	Heart, Artificial/	5,426
16	Implants, Experimental/	3,460
17	exp Heart Valve Prosthesis Implantation/	37,067
18	(percutan* aortic valve* adj (implant* or repair* or replace*)).ab,ti,kw.	329
19	(transcath* aortic valve* adj (implant* or repair* or replace*)).ab,ti,kw.	14,238
20	(aortic valve* adj (implant* or repair* or replace*)).ab,ti,kw.	29,946
21	((experimental or artificial or mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (heart or valv* or flap* or leaflet* or implant*)).ab,ti,kw.	28,035
22	((balloon-expand* or self-expand* or balloon expand* or self expand*) adj (TAVI or TAVR or PAVR)).ab,ti,kw.	238
23	((balloon-expand* or self-expand* or balloon expand* or self expand*) adj (transcatheter aortic valve implantation or transcatheter aortic valve replacement or percutaneous aortic valve replacement)).ab,ti,kw.	323
24	(TAVI or TAVR or PAVR).ab,ti,kw.	12,157
25	(transcatheter aortic valve implantation or transcatheter aortic valve replacement or percutaneous aortic valve replacement).ab,ti,kw.	15,011
26	or/14-24	94,856
27	(systematic review or meta-analysis).pt.	330,789
28	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	371,259

#	Query	Results from 29 Nov 2023
29	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	341,061
30	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	16,458
31	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	40,609
32	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	42,708
33	(handsearch* or hand search*).ti,ab,kf.	11,367
34	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	36,990
35	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	12,586
36	(meta regression* or metaregression*).ti,ab,kf.	15,379
37	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	491,979
38	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	360,633
39	(cochrane or (health adj2 technology assessment) or evidence report).jw.	21,758
40	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	18,217
41	(outcomes research or relative effectiveness).ti,ab,kf.	11,493
42	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	4,469
43	[(meta-analysis or systematic review).md.]	0
44	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	304
45	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	179
46	umbrella review*.ti,ab,kf.	1,703
47	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	14
48	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	18
49	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	12
50	or/27-49	716,632

#	Query	Results from 29 Nov 2023
51	Economics/	27,517
52	exp "Costs and Cost Analysis"/	267,609
53	Economics, Nursing/	4,013
54	Economics, Medical/	9,261
55	Economics, Pharmaceutical/	3,114
56	exp Economics, Hospital/	25,768
57	Economics, Dental/	1,921
58	exp "Fees and Charges"/	31,431
59	exp Budgets/	14,168
60	budget*.ti,ab,kf.	36,958
61	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	288,307
62	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	393,266
63	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	216,559
64	(value adj2 (money or monetary)).ti,ab,kf.	3,130
65	exp models, economic/	16,249
66	economic model*.ab,kf.	4,337
67	markov chains/	16,055
68	markov.ti,ab,kf.	29,914
69	monte carlo method/	32,528
70	monte carlo.ti,ab,kf.	61,558
71	exp Decision Theory/	13,518
72	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	40,123
73	or/51-72	920,727
74	13 and 26 and 50 and 73	60
75	13 and 26 and 50	1,572
76	limit 75 to yr="2020 -Current"	725
77	limit 74 to yr="2020 -Current"	21

Line 76: records were downloaded into an EndNote 21 library and exported to the clinical effectiveness reviewers for screening. Line 77: records were

downloaded separately into an EndNote 21 library and sent for screening for systematic reviews of economic evaluations and relevant economic models.

Lines 1-25 inclusive were adapted from the search for Evidence Review H in NG208 (line 25 was not used as it was redundant for this search). Line 43 was included in the scoping search for efficiency, it would have been removed for a more formal search as it is only relevant for APA PsycInfo on Ovid (as it is part of a multifile search this line is only relevant for APA PsycInfo on Ovid, which was not searched for this project).

Two search filters were applied to the search:

- *Systematic reviews - filter used*: A filter developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) (CADTH, 2021) to identify systematic reviews, meta-analyses, health technology assessments and indirect treatment comparisons was used. The CADTH filter is for multifile use on Ovid and was adapted for single database use in MEDLINE on Ovid.
- *Economic evaluations and economic models - filter used*: A filter developed by CADTH designed to identify economic evaluations and models was applied to the search strategy to identify systematic reviews in MEDLINE on Ovid (CADTH, 2016).