HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis

Draft Guidance themed comments

Relevance of NG208

Comment number	Name	Section number	Comment	Response
1	Consultee 1	1.3 What information is needed	We would like to state that the NICE NG208 economic model that was used for the cost-effectiveness of this Late-Stage Assessment was heavily criticised by both clinicians and industry in that consultation and thus the we feel the valve cost of £14,800 stated is not correct for all risk levels. You have not correctly stated the conclusions of NICE NG208 economic analysis for TAVI which are as follows: § TAVI is cost-effective for people at high-risk surgical risk at the current average list price of £17,500. In most scenarios, TAVI is highly cost effective and it becomes dominant when the price of a TAVI valve is reduced to £15,000. § TAVI is not cost effective for people at low or intermediate surgical risk at the current average list price of £17,500. If the price of the valve reaches £15,000, TAVI becomes highly cost effective for people at intermediate risk and at £14,800 it is cost-effective for people at low risk.	Thank you for your comment. The committee noted that the aim of this late-stage assessment was to determine whether price differences between transcatheter heart valves could be justified, and that it was outside the remit of this late-stage assessment to assess the cost effectiveness of TAVI compared with surgical valve replacement. So, references to the price thresholds for cost effectiveness of TAVI against surgery reported in NG208 have been removed from the guidance. See section 3.31 in the guidance.

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2	Consultee 6 Edwards Lifesciences	Not specified	Throughout the guidance document, there is very little or no justification (or explanation) of why there are major discrepancies between the conclusions of the analyses produced by the EAG, in comparison to the committee considerations and resulting draft guidance recommendations. This has led to the production of a draft guidance document which lacks logic, is confused in its reasoning and in some cases comes to conclusions based on evidence that has not even been presented to the committee. A clear example of this is in the economic modelling conducted by the EAG which bears no resemblance to the "what this means in practice" section of the draft guidance document. The reported NG208 model in the 'what this means in practice' section is not the economic analysis that was used by the committee in its decision making. Furthermore, the NG208 model is constructed using a comparator that was not in the scope of this LSA, devices that are no longer available to the NHS and models mixed valve types, which the EAG expressly said it did not do.	Thank you for your comment. The guidance document describes the considerations and discussions made by the medical technologies advisory committee, whose decision-making is based on evidence from the external assessment report, user preference report, a report by NICE's surveillance team and clinical, patient and procurement and commissioning expert feedback. The committee's discussion of the external assessment group (EAG's) work is outlined in section 3 of the guidance. The committee considered the relevance of the results from the economic modelling produced as part of NG208 during the third committee meeting. It noted that it was outside the remit of this late-stage assessment to assess the cost effectiveness of TAVI compared with surgical valve replacement. So, references to the price thresholds for cost effectiveness of TAVI against surgery reported in NG208 have been removed

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				from the guidance.. Please also see response to comment 1.
3	Consultee 6 Edwards Lifesciences	Not specified	Reasons given for not including RCT data included “surgery as a comparator, and often included older generation valves or valves no longer available in the NHS.” Please explain why it is considered appropriate to reference the economic model from NG208 which includes surgery as a comparator, includes older generations of valves and valves no longer available in the NHS, whereas RCTs were excluded from the assessment on the same basis	Thank you for your comment. The aim of this assessment was to determine whether price differences between transcatheter heart valves could be justified, and not to determine a cost-effective price for a transcatheter heart valve, which was evaluated in NG208. Therefore, the evidence requirements were different. Please also see response to comment 1

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4	Consultee 6 Edwards Lifesciences	Not specified	No, the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence and in the case of cost-effectiveness, the relative NMB findings reported by the EAG are unreported in the draft consultation document. The summary of cost-effectiveness and in particular the references to NG208 highlight clear examples of incomplete and ambiguous reporting and a consequent lack of transparency and fairness. There is a clear discrepancy in the cost-effectiveness presented in the draft guidance. The EAG decided that sAVR was not an appropriate comparator for this LSA and did not include it in their protocol, nor correspondingly in the EAG report. The draft guidance uses the unchanged model from NG208 which was not conducted using the data that was used in the EAG report, used mixed device expansion types and procedural approaches (combining data from transfermoral and transapical), and includes sAVR as a comparator. The committee was not presented with a comparison of TAVI with sAVR. Therefore, any reference to the clinical or the cost effectiveness of TAVi vs sAVR should be removed from this guidance. The EAG protocol clearly states that “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.” And in the EAG report that they "did not compare balloon- and self-expanding TAVI devices” This discrepancy between the EAG protocol and the final report conclusion of equivalence across valve types has not been explained.	Thank you for your comment. The relative net monetary benefit findings were not reported in the guidance as they were based on confidential price agreements provided by NHS supply chain. The final results cannot be reported publicly without breaching confidentiality. Please also see the response to comments 1 and 3. The EAG’s statement in the protocol indicates that it planned to compare devices within expansion types, so there is no discrepancy. No comparison between balloon-expanding devices was possible as only Sapien valves were available in the TAVI registry (although trial evidence for Myval was reported in section 5.2.1 of the assessment report and in the second addendum to the assessment report). The EAG compared self-expanding valves against each other which is

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				described in Table 25 and 26 of the assessment report (with associated text) and in the addenda to the assessment report.

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5	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This section (along with all other references to NG208) is highly misleading and should be removed. The analysis presented here is from a completely different dataset to that presented by the EAG. “What This Means in Practice” infers that it is the findings of the committee based on the EAG report that has informed this cost-effectiveness calculation and it is not, it is opinion and commentary based on a completely different dataset. The cost-effectiveness NG208 calculations shown here mixed the device expansion types, did not include the same TAVI registry data used by the EAG to inform its clinical inputs, included data from obsolete technologies, mixed surgical approaches and had sAVR as a comparator. The EAG also states that there is doubt over the relevance of this to the UK NHS population and it is very clear that the listed criteria were not used in their analysis. Irrespective of the flaws and inaccuracies, only two valves are specifically indicated for low-risk patients and as shown, these patients account for less than 10% of the patients treated with TAVI. If the objective is to compare clinical and economic outcomes among the TAVI valves, then high-risk patients should be considered and analysed as a distinct sub-population as this is the only common indications for all TAVI valves. If, despite the inaccuracies and flaws, NICE choses to keep references to NG208, it would be a very misleading omission and not helpful for commissioners to present this biased assessment of it, as the focus is on LR patients. NG208 concludes that TAVI in HR patients is highly cost-effective (the ICER is £7k / QALY) at a valve price of £17,500 and this has not been mentioned anywhere in the guidance.	Thank you for your comment. Please see response to comment 1 and 3.

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6	Consultee 6 Edwards Lifesciences	3.7 Availability of clinical evidence to address the decision question	Please explain why it is considered appropriate to reference the economic model from NG208 which includes surgery as a comparator, includes older generations of valves and valves no longer available in the NHS, whereas RCTs were excluded from the assessment on the same basis.	Thank you for your comment. Please see response to comment 1 and 3.
7	Consultee 6 Edwards Lifesciences	3.18 Model cost inputs	Section 3.18 This paragraph is highly misleading, biased and should be removed. All references to the economic model for NG208 should be removed as this uses a different comparator (sAVR) to this LSA EAG analysis, mixes valve types, mixes valve generations and was commented to be not appropriate for the UK NHS TAVI population (all of which were reasons given to reject RCTs). If, however, NICE insists on keeping the reference to NG208, despite the flaws and inconsistencies with other data reviewed and presented by the EAG, only reference to HR patients should be made as this is sole indication common to all valves. For HR patients, TAVI was found to be highly cost-effective with an ICER of £7,014 / QALY (considering a valve cost of £17,500) Considering a £20,000 WTP, most likely a valve at £27,500 would still be cost-effective.	Thank you for your comment. Please see response to comment 1.
8	Consultee 7 Boston Scientific	1.3 What information is needed	1. We support the observation that adjustments must be made for confounding factors, and suggest further clarity is provided around the importance of correcting analyses to account for selection bias. 2. We question why the cost effectiveness of TAVI as a whole vs SAVR (from a previous NICE assessment) has been brought into this section, when the Evidence Assessment Group chose not to compare TAVI with SAVR. Further, the quoted cost effective price of £14,800 or less is for all surgical risks; however as discussed during the committee meeting and identified in the Evidence Assessment Report, the vast	Thank you for your comment. Please see response to comment 1.

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			majority of TAVI procedures performed in the UK are for patients in the high and intermediate surgical risk category. Therefore, if the £14,800 figure is to be quoted, the cost effective prices for the intermediate and high surgical risk categories should also be quoted ahead of £14,800, to better reflect UK clinical practice.	
9	Consultee 9 Abbott Medical	1.3 What information is needed	Abbott would like to point out that surgery was removed as a comparator during the scoping workshop and therefore are unsure why it has been used as a comparator in the draft guidance.	Thank you for your comment. Please see response to comment 1.
10	Consultee 9 Abbott Medical	1.3 What information is needed	Abbott believes that this statement is misleading and does not reflect current TAVI usage in the UK. Abbott would like to point out that intermediate and low risk TAVI is not routinely commissioned in the UK and the mean age of patients undergoing TAVI in the UK remains at 80 years of age. Adding to this, many TAVI valves (including Navitor) are only indicated for use in high risk patients. Due to these reasons, Abbott does not believe that the low risk cost-effectiveness threshold should be stated here. Abbott suggests that one way around this would be to weight the cost-effectiveness threshold using the proportion high vs. low/intermediate risk patients currently being treated within the UK. This weighting would yield a price between £14,800 and £18,000 and would be more reflective of current practice in the UK.	Thank you for your comment. Please see response to comment 1.

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11	Consultee 10 Medtronic	1.3 What information is needed	We believe that this section is factually incorrect and misleading and gives the impression that a cost-effective price of £14,800 has been determined by this late-stage assessment. As mentioned in the paragraph this figure of £14,800 came from the NG208, 2021 clinical guideline on heart valve disease. It is inappropriate and misleading to quote this figure here for the following reasons: • The £14,800 price was the cost-effective price in NG208 for **low-risk patients only.** • This late-stage assessment draft guidance states that **TAVI is primarily used in people who are at high risk** for heart surgery or for whom surgery is inappropriate. **The cost-effective price for high-risk patients in NG208 was £18,000** therefore £14,800 is misleading and not representative of the majority of patients being treated. • **In NG208 an average price of £17,500** was used in the base case, and this was found to be **cost effective in high-risk patients at an ICER of £7,014**. • It is also important to note that the model from NG208 was designed to analyse the class effect of TAVI versus SAVR rather than the performance of individual valves versus SAVR. In Medtronic's EAR consultation response, we requested that SAVR be reinstated as a comparator; the EAG responded: ***"The agreed decision problem is based on selection of TAVI (when a clinical decision has been made that TAVI is appropriate); the role of LSA is not to repeat analysis of NG208 to determine cost-effectiveness of TAVI versus SAVR***. Whilst Medtronic still believe SAVR should have been included as a comparator as agreed in the scope, given the significant body of published evidence for TAVI vs. SAVR, it does appear contradictory and inappropriate to first exclude SAVR and then re-include with such a bold and misleading statement without having updated	Thank you for your comment. Please see response to comment 1.

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			the model to better align with the decision problem for this current Late-stage assessment • The EAG **did not update the cost or efficacy inputs to account for the significant body of new evidence or changes in costs since the analysis** was done for example, for the Evolut platform, 4-year RCT data is now published from the Evolut low risk trial (only 2-year follow-up was available for NG208). At euroPCR 2024 a cost-effectiveness analysis, based on this data, presented that Evolut TAVI is the only valve to demonstrate cost-effectiveness in low-risk patients in the UK incorporating 4-year outcomes. [redacted]. Medtronic agree that TAVI valves should be able to demonstrate cost-effectiveness in all patient populations before widespread access is granted in the NHS and we understand that the committee are keen to provide some quantitative direction for procurement purposes in line with the objectives of the LSA process. However, given the outdated, inaccurate and misleading nature of the current statement we suggest it is re-worded as follows: **"Previous analyses from the economic evaluation done for NICE's 2021 guideline on heart valve disease presenting in adults: investigation and management indicated that TAVI is cost-effective in high-risk patients at a valve price of £17,500 which represents most patients currently treated with TAVI in the NHS. However, the model also indicated that a transcatheter heart valve may need to cost £14,800 or less for the procedure to be cost effective in low-risk patients."**	

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12	Consultee 11 Meril UK	1 Recommendations	• £14,800 was indicated for low risk patients as an optimum price in NG208 high & intermediate risk was prices at higher levels – see below extracts. • NICE NG208 Economic analysis states 2.5.4 Cost of the valve In the base case scenario, the cost of a TAVI valve was assumed to be £17,500, which is the average price across the volume 80% of TAVI valves are purchased in England and Wales under the NHSE High-Cost Tariff Excluded Devices Programme. A second price of £15,000 was tested in the scenario analysis representing a realistic price reduction that may be achieved in the following years. In addition, a threshold analysis on the price of the valve is presented in section 3.3. 3.2.1 High risk In most scenarios, TAVI is highly cost effective and it becomes dominant when the price of a TAVI valve is reduced to £15,000. TAVI becomes not cost-effective when: • Historical and old trials are included in the meta-analysis estimating relative treatment effects • Mild PVLs are assumed to affect mortality • ICU and LOS are not scaled up for higher risk 3.2.2 Intermediate risk In most of the scenarios tested, TAVI is not cost effective compared to surgery. Although, if the price of the valve reaches £15,000, TAVI becomes highly cost effective for people at intermediate risk as well, confirming that the results of the model are extremely sensitivity to the price of the valve. 3.2.3 Low risk As with intermediate risk people, TAVI is not cost effective in most scenarios tested. If the price of a TAVI valve is reduced to £15,000, TAVI is cost effective at a threshold of £30,000 per QALY gained, though not at a threshold of £20,000 3.3 Threshold analysis	Thank you for your comment. Please see response to comment 1.

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			The results showed that for intermediate-risk patients, TAVI becomes cost effective at a threshold of £20,000 per QALY gained when the price drops below £15,500. For low-risk patients TAVI becomes cost effective at the same threshold when the price of the valve is reduced to £14,800 3.5 Limitations and interpretation The analysis demonstrated that TAVI is cost effective in patient at high surgical risk but not cost effective in patients at intermediate or low surgical risk compared to surgical aortic valve replacement. The sensitivity analysis shows that the results are extremely sensitive to the price of the TAVI valve. In a scenario where price is reduced to £15,000, TAVI would become cost effective in people at intermediate surgical risk and the same for the low-risk group at a price of £14,800. As discussed and negotiated with NHSE & NHS SC Meril entered the UK market as a cost effective treatment option from the start with Myval Octacor.	

Choice of evidence

Comment number	Name	Section number	Comment	Response
13	Consultee 1	Not specified	• We do not feel all relevant evidence has been taken into account: o The literature screening activity was too narrow and excluded key evidence that could have supported the comparable clinical effectiveness and durability of the valves. o The published clinical evidence seems to have been completely ignored in deference for the UK real world evidence. A better assessment would have been to validate the findings in the real-world data using the published evidence and vice versa. • The assessment did not include the clinical effectiveness comparison of self-expandable valves with balloon expandable valves which may have impacted on the economic evaluation, particularly on the in-hospital budget.	Thank you for your comment. The assessment report describes the literature search strategy and includes a review of the literature in the context of the decision problem. In addition, a summary of a further 44 studies has been described in addendum 1 to the assessment report. The EAG further reviewed 1,824 records identified through a systematic search, and 11 records identified through targeted searches, of which 10 were considered relevant to the scope and included in addendum 2 to the assessment report. The EAG explained the reasons for using UK real-world evidence to populate its economic model in the assessment report and further expanded on these reasons in the addenda to the assessment report. Both the report and the addenda set out the strengths and limitations of each approach. The committee's discussions on the evidence available to address the decision question are described in sections 3.6 to 3.10 in the guidance. The committee concluded that the UK TAVI registry was the most appropriate source of evidence, but

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				that it could not fully answer the decision question. The scope of this late-stage assessment was to assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation (TAVI) devices for people with severe aortic stenosis, to justify price variation and inform procurement decisions. This was not a features-based assessment (for example, the decision problem was not to compare the cost effectiveness of balloon expandable versus self-expanding devices), therefore the EAG reviewed evidence at a device level.
14	Consultee 1	Not specified	Considering that the assessments essentially only considered the real-world evidence and consequentially this supported only 4 of the 8 manufacturers' valves we agree that the summaries of clinical and cost-effectiveness are reasonable interpretations of the evidence used.	Thank you for your comment. The committee considered evidence on all of the valves included in the assessment. The committee's considerations on the valves not included in the UK TAVI registry dataset are outlined in section 3.12 of the guidance.

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15	Consultee 6 Edwards Lifesciences	Not specified	Our most serious concern, however, is that NICE has chosen to ignore over 8,000 (eight thousand) publications and yet concludes that “there is not enough evidence to support price variation” when this wealth of evidence, expert opinion, stakeholder advice and new evidence provided by us has been overlooked. The EAG state repeatedly in their report that for reasons of expediency, they did not take a more standard approach of assessing robust randomised controlled trials by conducting systematic literature searches and then using RWE such as the TAVI registry to complement evidence gaps. The EAG stated in response to a stakeholder comment on their report that “it is acknowledged that the evidence included in the report is not the entirety of the evidence available for each device” and that they had quite deliberately “removed the count of the number of papers and number of patients included in them” in order to “not cause confusion.” Far from causing confusion, failure to review the full evidence base for each device together with a lack of transparency in reporting what they did review is staggering. It would have added a great deal of clarity for the EAG to report transparently what evidence was reviewed to reveal the small subset of evidence upon which NICE has based its recommendations and the huge volume of data that has been ignored. Any lack of evidence review can only be as a result of the instructions given by NICE to the EAG about the appropriateness of producing an incomplete and expedited report and demonstrates the use of flawed HTA methods as numerous high quality, robust data and analyses were ignored for the sake of expediency. In a press release issued by NICE on August 9th (which despite assurances that it would be removed is still 'live' on Monday Sept 2nd), under the headline "No evidence to support price variation in heart valves used by the NHS" Prof Jonathan Benger is quoted as saying “We have looked for evidence to determine whether differences in innovation and performance between these valves can justify their range in price, but the information we have seen does not support the current variation in cost.” Prof Benger’s	Thank you for your comment. The EAG summarised a wealth of evidence from both published literature and real world sources on comparisons between transcatheter heart valves, which was considered by the medical technologies advisory committee. As described in the interim methods and processes statement for late-stage assessment, the EAG applied a pragmatic approach to the evidence review. However, in response to the resolution panel’s recommendation to review the decisions made on the evidence searching and selection, the EAG did a systematic search of published literature comparing the clinical effectiveness of all transcatheter heart valves included in this assessment. The committee concluded that the EAG’s original approach was reasonable and appropriate (see section 3.32 in the guidance). Based on all available evidence assessed, the EAG considered that patient-level real-world evidence from the UK on TAVI devices currently being used in NHS was the most relevant for the decision problem, as this enabled comparison of multiple TAVI devices whilst allowing adjustment for many

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			statement overlooks the fact that 'the information we have seen' is a small fraction of the available publications and so fails to acknowledge that not assessing the full evidence base has led to the production of wholly unsound recommendations and even more unreliable headlines and commentary.	known confounders. In its report, and in the addenda, the EAG set out the strengths and limitations of using real world data from a UK setting linked to routine outcome data, versus using data extracted from multiple separate published studies, to populate the economic model. Its conclusion was that neither approach fully addresses the decision problem, without bias or limitation, but that on balance, the linked UK real-world data was more applicable. A large amount of the available published evidence was not relevant to this late-stage assessment whose aim was to assess the incremental clinical, economic and non-clinical benefits of transcatheter heart valves to justify price variation and inform procurement decisions, due to but not limited to the following reasons: • Evidence comparing TAVI as a procedure with surgical valve replacement • Evidence on valves or generations of valves no longer on the UK market • Evidence on multiple valves where the device-specific

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				performance cannot be assessed • Non-comparative evidence • Evidence from contexts which were considered not to be generalisable to the NHS. The committee's discussions on the evidence available to address the decision question are described in sections 3.6 to 3.10 in the guidance. The committee concluded that the UK TAVI registry was the most appropriate source of evidence, but that it could not fully answer the decision question. We do not believe Prof Benger's statement to be incorrect, as the committee did conclude that it was unable to determine whether variations in cost were justified. However, the press release was retracted on 9 October 2024.

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16	Consultee 6 Edwards Lifesciences	Not specified	No, the vast majority of evidence has been ignored. There is a need for NICE to explain the conclusions of the committee of "insufficient evidence" which presumably is reached as a result of only a very small percentage of available TAVI publications being considered. There is an acknowledged flaw in compiling the evidence as there were no systematic literature reviews conducted – if they had done so, the EAG could have reduced limitation and avoided introducing bias. While the EAG claims to have "applied the hierarchy of evidence" they only included a total of 159 clinical studies in the EAG report (42 studies as key evidence being used, 58 studies considered in scope and rejected, a further 59 studies excluded). This compares with 764 references found when the EAG ran scoping searches designed to identify both systematic reviews of clinical effectiveness and systematic reviews of economic evaluations and economic models. A simple MedLine search conducted on 13th August 2024 returned 8,241 publications, 271 meta-analyses and 180 RCTs. There are also 62 published records of TAVI in the international HTA database which could have been drawn upon to support recommendations. Key data has been ignored due to time constraints or lack of understanding of the appropriateness of high-level studies which were recommended by experts as data generalisable to the UK. Edwards has repeatedly supplied published references to aid the decision problem to NICE before and during the official timeline of the TAVI LSA and in the EAG report consultation suggesting ways to incorporate data on thousands of patients distinguishing the various technologies by their indications, valve type and evidence availability. There is no logical explanation in the EAG report or replies to comments as to why much of this data has not been taken into account.	Thank you for your comment. Please see responses to comments 13 and 15.
17	Consultee 6 Edwards Lifesciences	Not specified	No, the recommendations are not sound, nor are they evidence based. The committee has not reviewed all relevant evidence and has been presented with inadequate cost effectiveness analyses to	Thank you for your comment. Please see responses to comments 13 and 15.

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			address the decision problem in this LSA. There is no sound basis upon which ANY recommendations can be made.	
18	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This sentence is misleading. It should state that more of the published available evidence for TAVI devices needs to be assessed and analysed before it can be determined whether price variation can be justified, or not justified, between different transcatheter heart valves. The current information reviewed shows that the data chosen by the EAG was not fit to answer the question and / or issue any evidence based guidance. All relevant evidence should have been reviewed.	Thank you for your comment. Please see response to comment 15.
19	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	It is hard to understand why there have been many global assessments of TAVI conducted using available data from RCTs, whereas NICE concludes otherwise. Experts have said that non-UK high-quality evidence is generalisable to the UK. The patients with sSAS are similar to other countries so high-quality published evidence should have been considered in the assessment	Thank you for your comment. This LSA aimed to assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation devices for people with severe aortic stenosis, to justify price variation and inform procurement decisions. In its assessment report and the addenda to the report, the EAG set out the limitations of available trial evidence, and real-world evidence, in answering the decision problem. The EAG explained that extrapolation of RCT evidence to real-world setting, and issues in combining RCT evidence due to lack of transitivity across all devices listed in the scope was also discussed in the protocol. During the committee meetings an expert adviser said that international

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				evidence is broadly generalisable to the NHS. But a specialist committee member noted that the level of TAVI use in the UK is lower than in many other higher-income countries, and that the populations may be different in terms of the proportions of people at different surgical risks (see section 3.7 of the guidance).
20	Consultee 6 Edwards Lifesciences	2.9 Sapien 3 and Sapien 3 Ultra (Edwards)	Taking the improvements of SAPIEN 3 Ultra as an example , if the assessment were truly looking at incremental innovation, it should provide detail of clinical outcome benefits seen from technology improvements and their associated economic value. This is demonstrated in controlled studies which were provided to the EAG but not reviewed.	Thank you for your comment. This LSA aimed to assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation devices for people with severe aortic stenosis, to justify price variation and inform procurement decisions. This was not a features-based assessment, and so the economic benefit of differences between device generations was not considered if previous generations are no longer available. Published evidence comparing Sapien 3 and Sapien 3 Ultra was summarised in section 5.2.1 of the assessment report, as well as the addenda to the assessment report, and comparisons from the UK TAVI registry in sections 5.3 to 5.5 of the assessment report. The committee's considerations on differences between generations are detailed in sections 3.11 and 3.14 of the

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				guidance. The committee concluded that the results of the UK TAVI registry were too uncertain to determine whether any differences in performance observed were because of features of the valves or the clinical characteristics of the people with aortic stenosis. Clinical experts stated that they consider different generations of valves from the same company to be largely equivalent.
21	Consultee 6 Edwards Lifesciences	3 3 Committee discussion	This statement is misleading as it was to unable assess the cost-effectiveness of the devices not captured in the UK TAVI Registry. The committee therefore could only consider evidence on 6 of the 11 devices. This should be clearly explained.	Thank you for your comment. The committee considered evidence on all of the valves included in the assessment. The committee's considerations on the valves not included in the UK TAVI registry dataset are outlined in section 3.12 of the guidance. The committee heard from NHS England representatives about the process of approval and addition of transcatheter heart valves onto NHS Supply Chain's TAVI framework.
22	Consultee 6 Edwards Lifesciences	3 3 Committee discussion	This statement is also misleading as the targeted review evidence was not used in the assessment as the Registry data only was used. It's important to explain that there was no systematic review of literature for each technology due to time constraints – the EAG acknowledged that it overlooked or ignored an abundance of publications. This is a procedural failure. All relevant evidence should have been identified and reviewed.	Thank you for your comment. The EAG outlines its approach to evidence searches in the protocol and external assessment report. The EAG's approach to evidence identification and synthesis was described in section 4.1.1. of the external assessment report, where the EAG noted that *"It was not*

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				feasible for the EAG to systematically search and sift evidence related to all older generations of TAVI devices for each manufacturer listed in the Final Scope. Instead, the EAG took a pragmatic approach, reviewing the published evidence provided by the Companies where more than 2 devices were compared." Pragmatic literature searches are permitted in the interim process and methods statement for late-stage assessment (see section 4.8) which states that the EAG can prioritise the studies or data it considers most valid and relevant to the decision problem presented in the scope (see section 4.9). Therefore, this does not constitute a procedural failure. However, in response to the resolution panel's recommendation to review the decisions made on the evidence searching and selection, the EAG did a systematic search of published literature comparing the clinical effectiveness of all transcatheter heart valves included in this assessment. The committee concluded that the EAG's original approach was reasonable and appropriate (see section 3.32 in the guidance). The clinical evidence review included both published evidence

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				and analyses of real-world data from the UK TAVI registry. Please also see response to comment 15.
23	Consultee 6 Edwards Lifesciences	3.6 Availability of clinical evidence to address the decision question	The data presented / considered by the EAG overlooks thousands of published studies , including hundreds of meta-analyses. Non-UK data (which the clinical experts indicated is generalisable to a UK setting) including randomized studies such as the PORTICO IDE trial published in the Lancet, the SCOPE I and II trials published in the Lancet and Circulation, and other meta-analyses were supplied during communication / consultation with NICE. All of these studies would have been found if there had been a systematic search. The TAVI registry was not set up to make between-device comparison and its lack of completeness makes it highly unreliable. Linked data was missing on a large percentage of patients and there is no data at all on several technologies under review. It is not clear why the data from over 100,000 patients in the network meta-analysis has been dismissed because of heterogeneity (Yang et al. 2023), or why some meta-analyses are missing such Takagi et al. 2019 for example. Yang et al clearly explains that the limitations (differences of aortic valve area, annulus diameter, annulus perimeter, annulus area, aortic angle and the extent of aortic valve calcification among individual patients and surgeon experience) are highlighted to explain moderate amount of heterogeneity in some of the analysis such as permanent pacemaker implantation, major vascular complications and major life threatening bleeding. The reviewer of this meta-analysis has not seen that the heterogeneity does not apply to outcomes such as mortality or stroke which are major cost drivers. In the Yang et al. 2023 meta-analysis, all RCTs and observational studies were assessed by using the Cochrane Collaboration's tool and Newcastle Ottawa Scale. Quality assessments were performed as well as various methodologies (frequentist and Bayesian) to	Thank you for your comment. Please see responses to comments 15 and 19. The EAG identified 4 network meta-analyses and summarised their limitations (see section 5.1 of the assessment report). It also described 5 systematic reviews in addendum 2 to the assessment report. The EAG highlighted that a key limitation was the inability to assume transitivity, which limits the internal validity of the analysis. For this reason, the UK TAVI registry was considered as the best available source of evidence for the economic model. The EAG reviewed and provided a summary of additional published evidence in addendum 1 to the assessment report. This included: - The study by Makkar et al. 2020 which summarised results from the PORTICO IDE non-inferiority trial compared Portico to other commercially available valves (Sapien, Sapien XT, Sapien 3,

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			validate the robustness of the findings. It is very difficult to understand why this piece of evidence and others are not seen as being as strong as the UK registry. While some of the TAVI technologies in the Yang et al meta-analyses have been removed, the data is still valid for those that remain and the results, along with other analyses, should be integrated in the assessment. It concludes that "SAPIEN 3 might be the best effective for decreased mortality and stroke" – these are two critical outcomes that should also drive the QALYs found in the EAG analysis and support the EAG NMB findings.	CoreValve, Evolut R, Evolut Pro; all combined). - The non-inferiority RCT by Tamburino 2020 which summarises results from the SCOPE II trial, which compared ACURATE neo (older model) with CoreValve Evolut R (older model). The EAG had included evidence comparing ACURATE neo2 and Evolut R/Pro in the assessment report. - The non-inferiority RCT by Lanz et al. 2019 summarised results from the SCOPE I trial which compared ACURATE neo to Sapien 3. The EAG had included larger studies which compared ACURATE neo2 to Sapien 3 within the assessment report. The network meta-analyses by Yang et al. 2023 and Takagi et al. 2019 were included in the assessment report. The committee considered their strengths and limitations and concluded the UK TAVI registry was the most appropriate source of evidence. The committee noted that clinically relevant confounding factors that were not captured in the UK TAVI registry were also not adjusted for in the key published evidence, and that RCTs often have selection bias.

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				None of the 5 systematic reviews included in addendum 2 were directly relevant to the decision problem, as all included combinations of valves or an earlier version of the valve in at least one arm. Please also see response to comment 19.
24	Consultee 6 Edwards Lifesciences	3.7 Availability of clinical evidence to address the decision question	The limitations expressed about RCT data can also be attributed to the UK TAVI registry, particularly devices that are no longer on the market, or an absence of data for those that are.	Thank you for your comment. The EAG limited the analysis of data from the UK TAVI registry to current TAVI device models as listed in the Final Scope, where the valve serial number was verified by the companies. For TAVI devices with no data in the registry, the best available published evidence was summarised. The committee recognised that both RCT and UK TAVI registry data were subject to bias, but that on balance the UK TAVI registry was the most appropriate source of data.
25	Consultee 6 Edwards Lifesciences	3.7 Availability of clinical evidence to address the	Edwards agrees that the RCT data are generalisable to the UK population and should be included in this assessment in order to make accurate comparisons and assessments of cost-effectiveness. Expert comments also reflect the findings from the UK TAVI registry and adds weight to why this assessment should focus on HR only. There are meta-analysis - specifically on HR patients - comparing	Thank you for your comment. The committee considered published evidence comparing clinical outcomes between different transcatheter heart valves in

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		decision question	short-term BEV vs. SEV outcomes that were mentioned many times and were completely overlooked (Senguttuven at al. 2023).	addition to the analysis of UK TAVI registry data. Regarding surgical risk levels, surgical risk is not currently recorded in the UK TAVI registry and cannot be robustly calculated retrospectively with the data that was available. The recommendations advise that surgical risk should be captured in future to better understand whether results are confounded by indication (see section 3.26), and that additional confounding factors should be captured which may allow for calculation of surgical risk. Clinical advice is that cardiologists do not consider surgical risk after the decision has been made by a multidisciplinary heart team to do TAVI, and that although most people having TAVI at the moment are at high surgical risk, transcatheter heart valves are sometimes used outside of their intended use when this is considered the most clinically appropriate option. The committee emphasised the importance of clinicians having control over which valve gets used for which patient by noting that the most clinically appropriate valve needs to be used. The revised guidance emphasises this point in recommendation 1.3.

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				The wording of the What information is needed section has also been amended to improve clarity around the value of recording surgical risk. The EAG considered Senguttuven et al. 2023 within addendum 1 to the assessment report. Senguttuven et al. 2023 compared balloon-expandable valves from 1 manufacturer with self-expandable valves from multiple manufacturers. Different generation devices were also combined. This is therefore unable to address the decision problem. Please also see response to comment 19.
26	Consultee 6 Edwards Lifesciences	3.7 Quality of UK TAVI registry data	While the sample size remains high, there is clearly an issue in basing guidance when only 53% of the patient outcome data is known. Not only is almost half of the potential data not available, there is unequal distribution among the various TAVI valves which are included. It is unsound of the committee to issue any guidance which is based on inherently biased and uncertain evidence	Thank you for your comment, it has been considered by the medical technologies advisory committee. The committee recognised that both RCT and UK TAVI registry data were subject to bias, but that on balance the UK TAVI registry was the most appropriate source of data.

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27	Consultee 6 Edwards Lifesciences	3.8 Quality of UK TAVI registry data	Comment: Out of the 7,409 procedures, 6,267 (85%) were linked to HES data. And among these 6,267 procedures, 4,710 (75%) were performed using the SAPIEN 3 / SAPIEN 3 Ultra device, 1,092 (17%) with the Evolut (R/Pro+) device but only 295 (5%) and 170 (3%) with Boston and Abbott respectively. This imbalanced sample size brings some important limitations in the ability to compare devices fairly (small sample size leads to wide confidence intervals). This is another reason why RCTs and meta-analyses provided should have been included in the assessment. The experts comment regarding the registry not being designed to make valve comparisons added to the complete imbalance of technologies reviewed and the absence of any data on almost half of the technologies in the LSA make it very difficult to understand why the registry data was felt fit for purpose.	Thank you for your comment. In the assessment report and in the addenda, the EAG set out the strengths and limitations of using real world data from a UK setting linked to routine outcome data, versus using data extracted from multiple separate published studies, to populate the economic model. Its conclusion was that neither approach fully addresses the decision problem, without bias or limitation, but that on balance, the linked UK real-world data was more applicable. The EAG did not assert that evidence from the literature was not fit for purpose, and by a similar argument, the consultee's assertion that the UK data is not fit for purpose should not follow. The EAG considered that patient-level real-world evidence from the UK on TAVI devices currently being used in NHS was the most relevant for the decision problem, as this enabled comparison of multiple TAVI devices whilst adjusting for known confounders. The limitation of combining multiple RCTs in network meta-analysis to enable comparison of multiple devices was described in the assessment report (see section 5.1).

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				The committee recognised the limitations of the analyses of data from the UK TAVI registry, but concluded that it represents the best available evidence to address this LSA's decision problem.
28	Consultee 6 Edwards Lifesciences	3.10 Results of UK TAVI registry analyses	The conclusions of the committee underline that making any recommendations based on this data is completely unsound. Additional clinical outcomes - statistically significant - showing difference among TAVI valves (from Table 21 in the EAG report) that should impact the cost-effectiveness and the NMB as well, but do not appear to have been taken into account: • Length of procedure and length of stay • Malposition of the valve • Use of post-implantation balloon dilatation • Major vascular complications • Stroke after discharge • Deaths (unadjusted comparison) • VARC-3 technical success (unadjusted comparison) • Need for bailout TAVI-TAVI (unadjusted comparison) If it is not possible to adjust for clinically important characteristics, then the weight of the missing confounders needs to be determined to explain the results. The EAG also underlines the issue with imbalanced sample size - leading to unfair comparison We do not understand why scenarios never seen in practice or in literature were used in the economic modelling (for example unrealistic predicted event proportions from the multivariate analysis considered for the base case – Table 27 from the EAG report). It is recognised by the EAG that they are "not fully comparable to the	Thank you for your comment. The EAG considered the following: • Length of stay: clinical experts advised that the numerical differences in length of stay between devices identified from the UK TAVI Registry were not clinically significant, and likely to reflect differences in practice between hospitals (rather than directly relevant to the valve itself). See page 109 and Table 21 of assessment report. • Length of procedure: whilst univariate differences were observed between devices, the Clinical Experts advised caution because this outcome may be influenced by differences in characteristics of patients receiving different TAVI devices and may not be directly linked to the TAVI device itself. See page 108/109 of 381 of the original

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			results from the published literature." and could have used RCTs to assess the validity of their model inputs	EAG report. Procedure duration was also considered in sensitivity analysis and had minimal effect on the cost effectiveness results; see Table 33 in the assessment report. • Malposition was not included in the analysis due to a very low event rate. See Table 21 in the assessment report. • Use of post-implantation balloon dilatation was included in the economic analysis (additional catheter cost, see Table 33 in the assessment report). • Major vascular complications, stroke and death after discharge were included in multivariable analysis (accounting for differences in patient characteristics between devices), however the EAG found no association with device (see Tables 23 and 24 in the assessment report). EAG consideration of major vascular complications is described in the assessment report (see page 150 of 381). • Both stroke and death were included in the economic model (see section 6.2.1 and model structure illustrated in Figure 11). • VARC-3 technical success is a composite outcome (only up to

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				exit from procedure room). The EAG considered aortic reintervention and readmission for heart failure longitudinally using the UK TAVI Registry in multivariable analysis. After adjusting for population differences between devices, no association between these outcomes and device used was identified; hence not included in economic analysis. See Table 24 in the assessment report. Scenario analyses were created incorporating feedback from Clinical Experts, see section 6.2.6 of the assessment report (wider sensitivity analysis are also described in section 6.2.5). The results of the multivariable analysis were reviewed by specialist committee members (SCMs). The point estimates of the multivariate modelling do not appear unrealistic; however the wide 95% confidence intervals are reflective of the small sample sizes for some devices and also rare events; and therefore reflect the uncertainty associated. Differences between real-world evidence and trial evidence were also highlighted in the published evidence. Deharo et al. 2020 stated "*Our real-life data showed that mortality was similar to, or slightly*

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				higher than, in the initial trials" (see addendum 1 to the assessment report).
29	Consultee 6 Edwards Lifesciences	3.11 Published evidence	This is a wholly inappropriate methodology which does not respect the hierarchy of evidence. By not undertaking the correct approach of conducting systematic searches for RCTs and meta-analyses, key evidence has been overlooked, or ignored when supplied to NICE. It also conflicts with the statement that there is "not enough evidence" in the recommendations and conclusions as there is clearly recognition that there is an abundance, most of which has not been considered. RWE should address any gaps in the abundance of published evidence and neither time pressure , nor volume of publications is not an acceptable reason for performing a sub-standard assessment.	Thank you for your comment. The EAG and committee considered the patient-level real world evidence from a UK NHS setting the most applicable to the decision problem (see section 5.1 of the assessment report and the addenda to the assessment report). Four network meta-analyses were described in section 5.1 of the

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			The method of pragmatic searches was introduced in the interim guidance several months (at the earliest March '24) after the LSA had commenced and the EAG had conducted its initial searches (Nov '23). We firmly believe that this pragmatic search method is unsound for the production of national guidance on medical technologies . As has been demonstrated in this LSA, it leads to thousands of publications being ignored. The RWE from the UK TAVI registry is extremely imbalanced with most of the data available coming from one specific category of TAVI devices (balloon-expandable valve in 72% of the UK TAVI registry and 75% once linked with HES data). The remaining evidence from self-expandable devices is also imbalanced, with a majority coming from the Evolut platform (19% and 17%) and only 5% or less are coming from the other 2 self-expandable platform (Boston and Abbott). This paragraph is also misleading as although 4 meta-analyses were considered, only one network meta-analysis was included (Yang et al. 2023)	assessment report. Yang et al. 2023 was prioritised due to its power and relevance to decision problem. Three of the studies reported the time periods for the included evidence: • Yang et al 2023 included evidence from inception through 1 February 2022. • Dogosh et al. 2022 included evidence from inception through August 2020. • Takagi et al. 2019 included evidence from inception through September 2018. The EAG summarised the key findings and limitations of the 4 network meta-analyses (see Table 5 in the assessment report). This LSA was launched in October 2023 and commenced scoping in alignment with the process outlined in section 2 of NICE's health technology evaluation manual. The scoping process for LSA was also referenced in the draft interim methods and process statement for LSA, which was later consulted on. However, there were no major amends to the respective section following consultation on the draft version that would have impacted this topic.

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				The EAG was asked to pause and not to conduct any analyses while the interim statement was being consulted on. The EAG was allowed to continue with background information gathering and work towards obtaining real-world data from the UK TAVI registry. Any changes to the interim statement following the public consultation would not have had an impact on the evaluation. NICE disagrees that there are thousands of publications being ignored, as not all publications describing TAVI are relevant to the decision problem. Please also see response to comment 15. In addition to the literature already included in the assessment report, the EAG considered an additional 44 studies identified by stakeholders at the consultation stages and summarized in addendum 1 to the assessment report. Two studies were considered most relevant to the decision problem. In response to the resolution panel's recommendation to review the decisions made on the evidence searching and selection, the EAG also did a systematic search of published literature comparing the clinical effectiveness of all

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				transcatheter heart valves included in this assessment. This identified 10 studies and 5 systematic reviews which were relevant to the scope. However, the EAG highlighted that none of the additional evidence changed the conclusions of the original assessment report. The committee concluded that the EAG's original approach was reasonable and appropriate (see section 3.32 in the guidance).
30	Consultee 6 Edwards Lifesciences	3.17 Model clinical inputs	The EAG needs to validate its assertion that using data from RCTs would give more biased results than the use of data from the TAVI registry and explain why they continued to use parameter inputs which "are not fully comparable to the results from the published literature." If RCTs could be used to inform the economic model (expert advisers) - why wasn't it done? Economic models is that they can cope with uncertainty, which is why DSA, PSA and scenarios analyses are performed. Validating the findings from the EAG with RCTs / meta-analysis and comparing with existing literature (eg Heathcote et al., 2023) would have been the right approach The TAVI registry does not have enough data on all 11 technologies, so to maintain a robust comparison, only SAPIEN / Evolut provide meaningful information.	Thank you for your comment. In the original report, the EAG included 3 RCTs: • Baumbach et al. 2024 where the comparator group had mixed valve type and generation. • Herrmann et al. 2024 included multiple generations of devices in both intervention and comparator arms, and was conducted in a population with small aortic annulus area only; • Thyregod et al. 2024 which compared TAVI to SAVR (included for longitudinal evidence for CoreValve up to 10 years). Within addendum 1, the EAG considered an additional 6 RCTs:

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				• 2 compared TAVI to SAVR (Forrest et al. 2023; Jorgensen et al. 2022). • 3 were non-inferiority trials and had mixed valve type and/or included older generations within arms (Lanz et al. 2019; Tamburino et al. 2020; Makkar et al. 2020a). • 1 was a 2x2 factorial equivalence RCT aiming to compare general anaesthesia with local anaesthesia and conscious sedation, as well as comparing self-expanding with balloon-expanding TAVI devices (Thiele 2020). The study was powered for equivalence of a composite outcome, and only reported outcomes to 30 days. The EAG considered that the identified RCTs were not directly relevant to the decision problem, and therefore did not include their short-term outcomes (between 30 days to 1 year) as a scenario in economic modelling. The EAG stated that other registry studies in TAVI have found differences with trial data, and that without an agreed method for resolution or evidence of process error, explanations of the differences between real-world evidence and trials are conjecture.

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				Heathcote et al. 2023 was included in the assessment report; this is a systematic review of economic evaluations of TAVI compared with medical management or SAVR and therefore not relevant to the decision problem. Within addendum 2, the EAG considered an additional 3 RCTs: • Terkelsen et al. 2025 • Feistritzer et al. 2025 • Nuche et al. 2023. The key limitations of randomised evidence as described in the assessment report and addendum 1 applied to those studies.
31	Consultee 6 Edwards Lifesciences	3.21 Justification for price variation	If the committee is unable to make any determination of the benefits of incremental innovations based on limitations of evidence, please explain what sound evidence is being used to base any guidance to the contrary. Certainly for five of the technologies there is a complete absence of evidence. Please explain how an absence of data, data with high uncertainty and data with significant bias can be used to issue any guidance. Please also explain how any conclusions can be drawn and guidance issued on the five technologies which have no data at all. This section reiterates the flawed logic and false conclusions of sections 3.13 and 3.14 and the lack of evidence based decision making	Thank you for your comment. The committee concluded that it was not possible to determine whether the differences in cost between valves were justified by benefits derived from incremental innovations. So, it recommended that valves should be chosen based on clinical appropriateness and value for money. It recognised the plausibility of clinical superiority of one valve over another and recommended the type of research needed for a technology to justify a higher price.

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				Please also see response to comment 21.
32	Consultee 6 Edwards Lifesciences	3.23 Evidence needed to demonstrate additional value	The committee drew this conclusion based on a very small percentage of the abundance of evidence that exists for TAVI technologies that was presented to them. Systematic searches and inclusion of relevant publications in the assessment would have presented a fairer picture of the true status of the available clinical evidence. It is a very unfair statement to say that more evidence is needed when there has not been a full assessment of the available evidence. The EAG acknowledges “that the evidence included in the report is not the entirety of the evidence available for each device” – a fair statement here would be to say that that the full evidence base should be assessed to conclude if more evidence is needed.	Thank you for your comment. Please see responses to comments 15, 21 and 22.
33	Consultee 6 Edwards Lifesciences	3.24 Evidence needed to demonstrate additional value	Existing data from published literature could and should be used to address uncertainties and to validate / correct the serious flaws in the model data input.	Thank you for your comment. Please see response to comment 30. The EAG justified and the committee accepted the reasoning behind not using trial data in the economic model (see section 3.18 of the guidance). The EAG highlighted that there is no evidence presented to support the assertion that the model input data had serious flaws. The assessment

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				report presented exploratory data analysis and univariate analysis to check the data, then validated the multivariate analysis against the exploratory data analysis and with SCM oversight.
34	Consultee 7 Boston Scientific	1.1 1 Recommendations	Overall Boston Scientific supports the committee's decision to recognise the multiple challenges, uncertainties, and caveats reported in the Evidence Assessment Report. However, statement 1.1 is not fully reflective of the discussions had, and currently risks misinterpretation. We wish to highlight that there is a wealth of high-quality evidence supporting TAVI. Further, a systematic literature review was not conducted for this assessment, limiting conclusions that can be made about evidence availability. We therefore suggest this first recommendation is reworded to reflect these points.	Thank you for your comment. See responses to comments 15, 21 and 22.
35	Consultee 10 Medtronic	Not specified	We are somewhat supportive of the draft recommendations and agree that the committee were not presented with enough evidence by the EAG, to draw solid conclusions on the decision problem as the wealth of published evidence for TAVI was excluded from the EAG analysis. This high volume, high quality, published evidence could have been very informative for the committee in addressing the decision problem and providing more constructive guidance to procurement bodies. Given the delays in this TAVI assessment to date, and time and resource constraints of the LSA process, we are not requesting a reassessment to include the large body of published evidence however we feel that some of the wording in the draft recommendations is misleading. We have made additional comments where we believe there are factual inaccuracies and statements open to misinterpretation that need to be corrected to ensure safe and effective, evidence-based care for patients with aortic stenosis.	Thank you for your comment. See responses to comments 15, 21 and 22.

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36	Consultee 10 Medtronic	1.1 1 Recommendations	We agree that the NICE committee were not presented with enough evidence in the EAG report to conclude whether price variations can be justified. However, if standard HTA methods had been applied and a systematic literature review (SLR) conducted by the EAG in line with the scope (i.e. including both alternative TAVI and SAVR as comparators), the committee would have been presented with a wealth of RCT evidence with long-term follow-up across different patient groups for some TAVI valve platforms and a dearth of RCT evidence for other valves – see **appendix 1** for an outline of these RCTs. We feel strongly that, had a different approach been taken, that the committee would have been able to assess the published evidence for each valve platform and draw conclusions regarding the differentiated value. Given that the EAG did not perform SLR, largely excluded all published evidence and instead relied on the UK TAVI registry, we feel that recommendation 1.1 should include the underlined additional wording for clarity as follows: 1.1 There is not enough evidence **from the UK TAVI registry** to determine whether incremental innovations can justify price variations between different transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in adults with aortic stenosis. Appendix 1. Outline of the RCT evidence published for each valve platform.	Thank you for your comment. See responses to comments 15, 21 and 22. Regarding evidence for previous generations of valves with long-term follow-up, the committee considered the longest available follow-up data for each valve family. The committee noted that older data can be less relevant because of differences in the population, clinical pathway and transcatheter heart valves themselves, and concluded that the availability of long-term data for a valve family does not justify a higher price for current iterations. Please see sections 3.15 and 3.23 of the guidance.

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			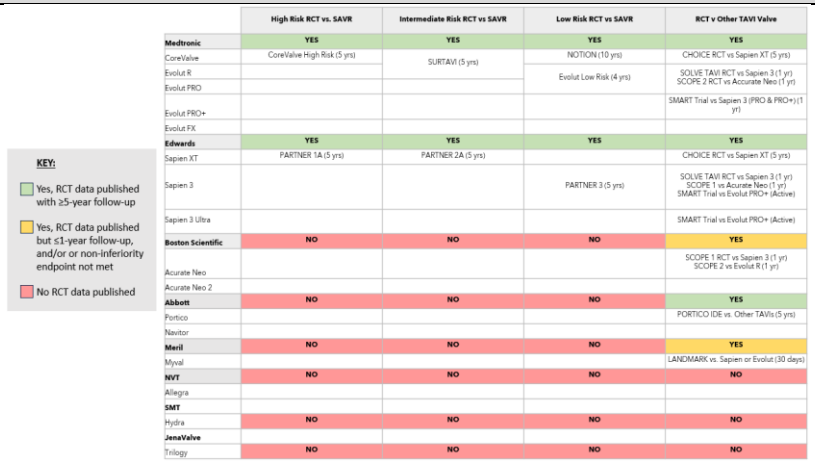	
37	Consultee 12 Heart Valve Voice	1 Recommendations	Heart Valve Voice, a charity with nearly a decade of experience supporting individuals with heart valve disease, would like to express its deep concerns regarding the recent recommendations from NICE on LSA heart valve treatment options. While we fully support the goal of ensuring the NHS delivers both high-quality and cost-effective care, we believe the current recommendations do not fully reflect the evidence presented which, through many other stakeholders, have provided throughout the consultation process.	Thank you for your comment, it has been considered by the medical technologies advisory committee.
38	Consultee 12 Heart Valve Voice	Not specified	We are particularly troubled by the inconsistency between the recommendations and the evidence presented. The conclusions reached appear to be based on insufficient comparative data between the different Transcatheter Aortic Valve Implantation (TAVI) valves available. Without robust, head-to-head comparisons, it is difficult to confidently make decisions that could affect patient care and outcomes. As we have advocated throughout the process, patient care decisions, especially those involving complex heart valve selection, must be driven by rigorous, high-quality evidence,	Thank you for your comment. The committee's recommendations were based on a substantial evidence review and feedback from clinical, patient and procurement and commissioning experts. The committee's considerations included patient safety. The committee noted that all the valves included in the assessment have Class III CE

	High Risk RCT vs. SAVR	Intermediate Risk RCT vs SAVR	Low Risk RCT vs SAVR	RCT v Other TAVI Valve
Medtronic	YES	YES	YES	YES
CoreValve	CoreValve High Risk (5 yrs)	SURTAVI (5 yrs)	NOTION (10 yrs)	CHOICE RCT vs Sapien XT (5 yrs)
Evolut R			Evolut Low Risk (4 yrs)	SOLVE TAVI RCT vs Sapien 3 (1 yr) SCOPE 2 RCT vs Accurate Neo (1 yr)
Evolut PRO				
Evolut PRO+				SMART Trial vs Sapien 3 (PRO & PRO+) (1 yr)
Evolut FX				
Edwards	YES	YES	YES	YES
Sapien XT	PARTNER 1A (5 yrs)	PARTNER 2A (5 yrs)		CHOICE RCT vs Sapien XT (5 yrs)
Sapien 3			PARTNER 3 (5 yrs)	SOLVE TAVI RCT vs Sapien 3 (1 yr) SCOPE 1 vs Acurate Neo (1 yr) SMART Trial vs Evolut PRO+ (Active)
Sapien 3 Ultra				SMART Trial vs Evolut PRO+ (Active)
Boston Scientific	NO	NO	NO	YES
Acurate Neo				SCOPE 1 RCT vs Sapien 3 (1 yr) SCOPE 2 vs Evolut R (1 yr)
Acurate Neo 2				
Abbott	NO	NO	NO	YES
Portico				PORTICO IDE vs. Other TAVIs (5 yrs)
Navitor				
Meril	NO	NO	NO	YES
Myval				LANDMARK vs. Sapien or Evolut (30 days)
NVT	NO	NO	NO	NO
Allegra				
SMT				
Hydra	NO	NO	NO	NO
JenaValve				
Trilogy	NO	NO	NO	NO

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			and any recommendations that oversimplify these decisions risk jeopardising patient safety.	certification which is supported by evidence of safety and performance. Additionally, the committee heard that NHS Supply Chain operates a phased introduction of new valves to look for any safety signals. The committee concluded that the valves available on NHS Supply Chain have enough evidence to be used in the NHS, but that the available evidence does not allow for direct comparison between different valves (see section 3.12 in the guidance).

Equivalence and comparability

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39	Consultee 6 Edwards Lifesciences	Not specified	Edwards have previously advised that to determine whether price differences between TAVI devices are justified, NICE could and should have created ICERs for each technology. It is clear from the EAG report's conclusions that TAVI devices cannot be assumed to be equivalent, therefore it is wrong and methodologically flawed to cluster them and use an assumption that devices are clinically equivalent to develop cost minimisation recommendations. TAVI devices are clearly not clinically equivalent.	Thank you for your comment. The EAG did not assume equivalence both in its clinical assessment and in the economic evaluation. The clinical parameters in the economic evaluation were based on observed event proportions from the real-world data and are reflective of true device performance. Incremental cost effectiveness ratios can only be used for pairwise comparisons. The EAG used net monetary benefits in order to allow multi-device comparisons. The committee did not conclude that the available valves were clinically

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				equivalent but that the uncertainty was too high to attribute any substantial incremental differences to a particular valve, so the choice of valve is recommended to be made based on both clinical appropriateness and value for money (see sections 1 and 3.13 of the guidance).
40	Consultee 6 Edwards Lifesciences	1.2 1 Recommendations	This recommendation has no evidential basis. The absence of evidence of non-equivalence cannot be used to justify an assumption of equivalence. In order to recommend the least expensive option, clinical equivalence between valves needs to be established with a high degree of confidence. The ERG have concluded, and the committee have clearly stated, that clinical equivalence cannot be assumed. That being the case, this recommendation is unreasonable in the light of the evidence. The terms “Least expensive option” and “clinically appropriate” lack any definition to guide clinicians on which valves are clinically appropriate and in which circumstances. At the very least there needs to be a clear explanation of whether this wording means they should use the cheapest device, the TAVI device which is the most cost-effective or the device which leads to the least expensive procedure overall, taking into account all associated costs such as those of adverse events. “Clinically appropriate” should also include the requirement for the device to have regulatory approval and a robust body of evidence to support its use. The EAG summarised that there was an “inability to assess the cost-effectiveness of the devices not captured in the UK TAVI Registry.” 5 out of 11 TAVI devices didn’t have any data from the UK registry, there were significant imbalance in sample sizes for those that did and some devices had no long-term evidence. This recommendation could be interpreted to mean that any of the 5 should be chosen despite not having any data because it would be the least expensive option. NICE would be putting patients at	Thank you for your comment. The wording of the recommendation has been amended to highlight that clinical appropriateness should be a consideration when choosing a valve. Please also see responses to comments 38 and 39. The committee also noted that patients are typically not able to choose the specific valve that they receive, but they value having information about the factors influencing valve choice, so that they can better understand the reasoning. Clinicians will have to justify their choice of valve based on clinical appropriateness and will therefore be able to communicate this to patients clearly as part of shared decision making.

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			potentially considerable risk as the least expensive may not be within a licensed indication and / or may have no long-term data to establish the clinical performance of the technology. It also completely disregards the patients' opinion and doesn't give them fully informed shared decision making opportunities.	
41	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	The document states that clinical equivalence cannot be assumed, so there is flawed logic in the assumption of clinical comparability. The word "likely" is indicative that this is speculative judgement and not an evidence based statement. A wider review of the evidence base would reveal that there are material differences in the clinical performance of TAVI valves.	Thank you for your comment. The committee agreed that clinical equivalence cannot be assumed, but concluded that there was not enough evidence to justify price differences between valves. As many valves could be considered clinically appropriate for most people with aortic stenosis, it recommended that value for money should be a consideration when choosing a valve.
42	Consultee 6 Edwards Lifesciences	3.13 Clinical comparability between companies	This is a flawed and illogical conclusion. If "clinical equivalence cannot be assumed" then the assertion that the "valves are clinically comparable" is false. The word "likely" is highly ambiguous and unhelpful – this is another example of a non-evidence based statement which is misleading. By definition, if clinical equivalence cannot be assumed, then there is no data upon which to make any recommendation or any comparison between devices in this class of products. Not only can there be no comparison of incremental innovations, there can be no comparison of the economics or of their price. Recommendation 2 is not supported by any data or analysis. Despite the statement in the document "clinical equivalence cannot be assumed" recommendation 2 automatically and incorrectly assumes that there is equivalence between devices, five of which had no data on which to base any assessment.	Thank you for your comment. The wording of the guidance has been amended to remove the ambiguity related to the term "clinically comparable". The committee recommended the use of a valve that is clinically appropriate and value for money (see sections 1.2 and 1.3 of the guidance). Please also see responses to comments 21, 38 and 41.

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43	Consultee 10 Medtronic	1.2 1 Recommendations	We also suggest that an additional recommendation is added to reflect the committee's conclusion that "Clinical equivalence between companies' valves could not be assumed" [Section 3.13] and "companies should be able to show… clinical noninferiority if they are introducing a new valve or a new generation of the technology with minor improvements to the market" [Section 3.23] **1.4 New valves should have evidence to show that they work at least as well as other valves**	Thank you for your comment. The Why the committee made these recommendations section states that "If a new valve costs more, this should be justified with evidence showing that it works better than existing valves". Please also see responses to comments 21 and 38.
44	Consultee 10 Medtronic	3.13 Clinical comparability between companies	Section 3.13 reads as follows: "The committee recalled that for most people with aortic stenosis, many of the available valves could be used (see section 3.3). So, it is likely that for those people the valves are clinically comparable" **We recommend that the specialist committee members and/or expert advisors are asked to confirm the accuracy of this statement** since we are surprised that TAVI implanters would agree that the evidence for "many" of the 11 TAVI valves included in this assessment is sufficient to be used in "most people with aortic stenosis". We feel the low volume usage of certain valves in the NHS would indicate otherwise. Also, we feel that the underlined section is more of an assumption than factual statement and appears to contradict other statements from specialist committee members and expert advisors such as: • **"Clinical equivalence between companies' valves could not be assumed" [Section 3.13]** • **"companies should be able to show… clinical noninferiority if they are introducing a new valve or a new generation of the technology with minor improvements to the market" [Section 3.23]** Published RCT evidence also demonstrates that it cannot be	Thank you for your comment. Please see responses to comments 41 and 42. Clinical experts advised that the decision about which type of transcatheter heart valve to use is usually made by an interventional cardiologist as part of a multidisciplinary heart team, and largely depends on the clinical characteristics of the person with aortic stenosis. The decision may also be related to the clinician's experience with a particular transcatheter heart valve or the range of valves that are locally available. The EAG included Tamburino 2020 and Lanz 2019 in addendum 1 to the assessment report. Herrmann et al. 2024 was included in the assessment report.

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			assumed that valves are clinically comparable: • Transfemoral transcatheter aortic valve replacement with the self-expanding ACURATE neo did not meet noninferiority compared with the self-expanding CoreValve Evolut in terms of all-cause death or stroke at 1 year. The ACURATE neo was associated with more moderate or severe aortic regurgitation at 30 days and cardiac death at 30 days and 1 year (Tamburino et al., 2020). • TAVI with the self-expanding ACURATE neo did not meet non-inferiority compared to the balloon-expandable SAPIEN 3 device in terms of early safety and clinical efficacy outcomes (Lanz et al., 2019) • Among patients with severe aortic stenosis and a small aortic annulus who underwent TAVR, a self-expanding supraannular valve was noninferior to a balloon-expandable valve with respect to clinical outcomes and was superior with respect to bioprosthetic-valve dysfunction through 12 months (Herrmann et al., 2024) References: • Tamburino C etal., Comparison of Self-Expanding Bioprostheses for Transcatheter Aortic Valve Replacement in Patients With Symptomatic Severe Aortic Stenosis: SCOPE 2 Randomized Clinical Trial. Circulation. 2020 Dec 22;142(25):2431-2442. doi: 10.1161/CIRCULATIONAHA.120.051547. Epub 2020 Oct 15. PMID: 33054367. • Lanz, Jonas et al., Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial, The Lancet, Volume 394, Issue 10209, 1619 – 1628 • Herrmann HC, Mehran R, Blackman DJ, Bailey S, Möllmann H, Abdel-Wahab M, Ben Ali W, Mahoney PD, Ruge H, Wood DA, Bleiziffer S, Ramlawi B, Gada H, Petronio AS, Resor CD, Merhi W,	

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			Garcia Del Blanco B, Attizzani GF, Batchelor WB, Gillam LD, Guerrero M, Rogers T, Rovin JD, Szerlip M, Whisenant B, Deeb GM, Grubb KJ, Padang R, Fan MT, Althouse AD, Tchétché D; SMART Trial Investigators. Self-Expanding or Balloon-Expandable TAVR in Patients with a Small Aortic Annulus. N Engl J Med. 2024 Jun 6;390(21):1959-1971. doi: 10.1056/NEJMoa2312573. Epub 2024 Apr 7. PMID: 38587261.	

Clinical appropriateness

Comment number	Name	Section number	Comment	Response
45	Consultee 6 Edwards Lifesciences	1.3 1 Recommendations	Additionally, criteria need to be developed to allow clinicians and patients to reach an evidence based, informed choice in deciding which valve is clinically appropriate.	Thank you for your comment. The guidance has been amended to provide additional recommendations for healthcare professionals.
46	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	This is clear recognition that there is uncertainty around clinical performance of newer technology, yet these could fall into the “least expensive” category. Without proof of performance and proper economic evaluation of all valves in the LSA, no guidance should be issued as it’s impossible to judge from the guidance which is or isn’t clinically appropriate. demonstrated by the fact that NICE have not developed any criteria to inform a ‘clinically appropriate’ choice.	Thank you for your comment. The committee recognised that the most clinically appropriate valve will differ for every person with aortic stenosis and will be influenced by the characteristics of the person. Please see responses to comments 21 and 38.
47	Consultee 9 Abbott Medical	1.3 1 Recommendations	Abbott welcomes this recommendation as it is focused on clinical appropriateness.	Thank you for your comment, it has been considered by the medical technologies advisory committee.

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48	Consultee 10 Medtronic	1.2 1 Recommendations	Recommendation 1.2 states: “Use the least expensive option available that is clinically appropriate for TAVI in the person with aortic stenosis”. We have received feedback from customers that NICE are suggesting that the cheapest valve should be used and they appear to miss the relevance of “clinically appropriate”. This could be a risk to patients, especially if/when new TAVI valves come to the market without sufficient evidence. To avoid misinterpretation, we suggest recommendation 1.2 is reworded as follows: **1.2 Use the least expensive, clinically appropriate, option for TAVI in the person with aortic stenosis, based on published evidence.**	Thank you for your comment. The structure and wording of the recommendations has been amended to emphasize the importance of using a clinically appropriate valve for each person with aortic stenosis who has been selected for TAVI (section 1.2 of the guidance).
49	Consultee 12 Heart Valve Voice	Not specified	Heart valve selection is a nuanced process that requires the expertise of multidisciplinary teams (MDTs), and reducing these decisions to a question of cost-effectiveness alone undermines the individualised care that patients require. We believe that any assessment of heart valve devices must consider the unique clinical needs of each patient, and recommendations should not be made based on incomplete or inadequate data.	Thank you for your comment. The committee recommended the use of a valve that is clinically appropriate as well as value for money. The factors that determine clinical appropriateness have been described in in the section on healthcare professional considerations.

Wording of guidance

Comment number	Name	Section number	Comment	Response
50	Consultee 1	Not specified	Yes, we consider the recommendations sound, and a suitable basis for guidance to the NHS.	Thank you for your comment, it has been considered by the medical technologies advisory committee.
51	Consultee 1	3.24 Evidence needed to	We agree the UK TAVI Registry needs to be redesigned to include information that allows for a comparison of valves. However, the collection, analysis, publication, resourcing,	Thank you for your comment. Guidance developed within the HealthTech Programme can advise on the value of

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		demonstrate additional value	responsibility and access also needs to be addressed as these have been a contributory factor to its inadequacy.	medical technologies, in particular on their use and future evidence generation. It is beyond the programme's remit to provide operational guidelines to other stakeholders. The committee considered how its recommendations can affect data collection in the UK TAVI registry (see sections 1 and 3.15 of the guidance).
52	Consultee 3 JenaValve Technology GmbH and JenaValve Technology Inc.	1.2 1 Recommendations	Clinician authority and autonomy to apply their subject matter expertise and professional experience is of primary importance in achieving optimal treatment outcomes for UK patients. The Committee's consideration of minority groups, including that of AS pathology, is mindful and inclusive in this discussion and decision process. JenaValve would like to highlight the prognostic importance of device selection and note that there are 7,868 severe, symptomatic AS patients due to native leaflet thickening with minimal calcification (15.4% of severe, symptomatic AS TAVI eligible patients) in the UK right now. We appreciate the Committee for respecting clinician choice to utilize Trilogy as the TAVI of choice of UK clinicians for this severe AS patient minority. References for the numeric values and preference statements above are derived from the following published medical literature: Strange GA, Stewart S, Curzen N, et alUncovering the treatable burden of severe aortic stenosis in the UKOpen	Thank you for your comment, it has been considered by the medical technologies advisory committee.

Comment number	Name	Section number	Comment	Response
			Heart 2022;9:e001783. doi: 10.1136/openhrt-2021-001783 Xiong TY, Feng Y, Liao YB, Li YJ, Zhao ZG, Wei X, Xu YN, Wei JF, Peng Y, Piazza N, Mylotte D. Transcatheter aortic valve replacement in patients with non-calcific aortic stenosis. EuroIntervention. 2018 Feb 2;13(15):e1756-63 Abramowitz, Y., Jilaihawi, H., Pibarot, P., Chakravarty, T., Kashif, M., Kazuno, Y., Maeno, Y., Kawamori, H., Mangat, G., Friedman, J., Cheng, W., & Makkar, R. R. (2017). Severe aortic stenosis with low aortic valve calcification: characteristics and outcome following transcatheter aortic valve implantation. European heart journal. Cardiovascular Imaging, 18(6), 639–647. Claessen BE, Tang GHL, Kini AS, Sharma SK. Considerations for Optimal Device Selection in Transcatheter Aortic Valve Replacement: A Review. JAMA Cardiol. 2021;6(1):102–112. doi:10.1001/jamacardio.2020.3682 Ali N, Blackman DJ. (2019) TAVI: Which valve for which patient? Cardiac Interventions Today. 13(2): 72-78.	
53	Consultee 4	1.3 What information is needed	"the person's surgical risk" is incorrect. Surgical risk is commonly used as referring to the risk of surgical AVR, not TAVI. If this phrase is required, it should be changed to "the person's risk for TAVI". The risk for surgical AVR is not relevant to the risk for TAVI.	Thank you for your comment. Surgical risk is discussed as it forms part of the intended use of different transcatheter heart valves. During the second committee meeting the committee reflected on the value of recording and adjusting for a person's surgical risk in future research in order to determine if the use of different valves is confounded by indication It concluded that there is value in knowing the person's surgical risk in future research. The wording of section 1 has been amended to improve clarity.

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54	Consultee 4	3.4 Choice of valve	I think "tricuspid valve anatomy" is better replaced with "trileaflet valve anatomy" - to prevent confusion with the tricuspid valve	Thank you for your comment. The wording of the guidance has been amended as suggested.
55	Consultee 5	Not specified	The most cost effective device should be used where appropriate but consideration should be given to Operator experience and Complication rates. We should be aware that inexperienced/training operators may find some devices more challenging to deploy and prefer a particular type, there seems to be little published evidence on this aspect of TAVI. The accepted complication rates are "low" at 1%, predominantly migration/embolisation most requiring Emergent Cardiac Surgery with a high complication rate not to mention vascular access issues. There is some published evidence that some TAVI products migrate more than others, although it is likely that some migration may be linked to operator experience (personal observations). There seems to be little published evidence concerning TAVI in general. I suggest that the UK TAVI database is interrogated at intervals to provide the data that we need to recommend TAVI products and this guidance amended appropriately. Perhaps new devices coming to the market should be trialled at a specific UK centre initially. I comment as a Patient voice and from that perspective I regard a 1% serious complication rate as uncomfortable and this should be clearly communicated to a patient at shared	Thank you for your comment. All companies provide training on their technology for interventional cardiologists. In addition, operator learning curve was acknowledged as a confounder of analysis (see section 5.3.1 of the assessment report). The committee considered the most relevant outcomes and recommended that future research should capture mortality, stroke, paravalvular leak or aortic regurgitation, permanent pacemaker implantation, reintervention, the specific valve used and the person's surgical risk.

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			decision making. Although patients will be lead by consultant opinion. Surgery should not be marginalised. I would like to think that a cardiologist would be able to use a device that he/she is comfortable and experienced with deploying. [redacted]	
56	Consultee 6 Edwards Lifesciences	Not specified	This sentence appears to suggest that there is a separate piece of guidance being created on "using transcatheter heart valves for aortic valve implantation" in addition to the LSA. There is nothing in the current published NICE programme of work that supports this statement. Please provide further details, or clarity, on ongoing additional guidance creation.	Thank you for your comment. This wording refers to this LSA and not to a different piece of guidance. It was included to explain the purpose of consultation and is not in the final guidance.
57	Consultee 6 Edwards Lifesciences	Not specified	NICE should also make it clear early in the guidance and the recommendations that five of the eleven technologies have no evidence at all to make a valid comparison. It is our firm belief that these technologies should not form part of the guidance recommendations or have only “in research” recommendations for their use, until such time that they develop an evidence base suitable for HTA. Doing otherwise undermines the work that many other companies do to generate evidence for value assessment.	Thank you for your comment. The committee considered evidence and feedback from clinical, patient and procurement and commissioning experts which covered all technologies included in this LSA. The committee’s recommendations cover all transcatheter heart valves currently available for use in the NHS. Please also see responses to comments 21 and 38.
58	Consultee 6 Edwards Lifesciences	Not specified	There is a general problem in issuing guidance to use the “least expensive” when there is no clinical evidence for doing so for 5 out of 11 of the technologies. Careless and ill-thought out recommendations, not based in evidence, could introduce risk to the whole TAVI patient population.	Thank you for your comment. Please see responses to comments 21, 38 and 57.

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59	Consultee 6 Edwards Lifesciences	Not specified	There are numerous examples where the document has not accurately summarised the views and evidence presented that will be presented in these comments. One instance is that the evidence on 5 out of 11 devices is unknown, which contradicts section 3 of the document which asserts that the committee reviewed evidence and made decisions on price justification on 11 devices.	Thank you for your comment. Please see responses to comments 21, 38 and 57.
60	Consultee 6 Edwards Lifesciences	Not specified	From the EAG analyses and report, one technology, SAPIEN 3, clearly maximises the clinical effectiveness and the value for money (NMB). This is supported by the findings from the literature from both a clinical and economic perspective [Senguttuvan et al , Front Cardiovasc Med. 2023 May 25;10:1130354 and Heathcote et al, Clinicoecon Outcomes Res. 2023; 15: 459–75.- both previously supplied]. Despite the EAG findings, this LSA draft guidance states that "the committee agreed that it is not possible to establish whether the differences in net monetary benefit were because of differences in valve performance or because of confounding in the clinical data used to inform parameters in the economic model." It therefore follows that there is insufficient evidence to draw any conclusions, as the EAG has only been able to produce an economic model which has "significant bias" and is "highly uncertain." Please explain how is it possible to make the recommendation to use the "least expensive option available which is clinically appropriate" when the guidance states that the committee have indicated that it was not possible to establish the reasons for differences in NMB?	Thank you for your comment. Although it could not be shown publicly due to confidential pricing agreements, the net monetary benefit confidence intervals overlapped significantly between valves (see section 3.20 of the guidance). Please also see responses to comments 30 and 31.

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61	Consultee 6 Edwards Lifesciences	1.1 1 Recommendations	Recommendation 1.1 is very misleading as it is unknown whether the lack of evidence to make any determination is due to the inadequate level of data searches and analysis conducted. A more correct statement would be that evidence the EAG chose to assess did not provide enough information to draw any conclusion on the appropriateness of price variations. , It is particularly worrying that guidance recommendations include devices where there was an "inability to assess the cost-effectiveness of the devices not captured in the UK TAVI Registry" - almost half of the technologies in the assessment. Recommendation 1.1 is also not a fair reflection of the conclusion of the committee that "it is not possible to establish whether the differences in net monetary benefit were because of differences in valve performance or because of confounding in the clinical data." This statement indicates the possibility that differences in NMB could have been due to differences in valve performance. In the summary of the results presented the EAG "does not exclude the possibility that they reflect the true performance of the TAVI devices." It is not a reasonable conclusion to make a recommendation based on an argument that there isn't enough evidence. Due to the differences in regulatory indications, the lack of comparison across valve types and committee conclusion that equivalence cannot be assumed between devices there should not be a recommendation issued on variations between device types or on "aortic stenosis" as a blanket indication Consideration should be given to conducting the LSA for high-risk patients by different device type – the overwhelming majority of TAVI procedures - where there is a common ground from a regulatory perspective and an abundance of data.	Thank you for your comment. Please see responses to comments 14, 15, 25, 31 and 60.

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62	Consultee 6 Edwards Lifesciences	1.3 What information is needed	The clinical outcomes listed are captured in the UK TAVI registry. The issue with relying on the TAVI registry for comparative effectiveness evaluation is the number of patients per device in the registry which differs dramatically between devices - making such comparison almost impossible and in 5 of 11 cases unknown.	Thank you for your comment. The wording of the respective section has been amended to clarify that the listed outcomes should be collected in both primary studies or secondary analyses of real-world data sources.
63	Consultee 6 Edwards Lifesciences	1.3 What information is needed	With all the comorbidities included in the UK TAVI registry, a calculation of the person's surgical risk (EuroScore, STS) should be possible	Thank you for your comment, it has been considered by the medical technologies advisory committee. The wording of the respective section has been amended to clarify that the listed outcomes should be collected in both primary studies or secondary analyses of real-world data sources. Please also see response to comment 25.
64	Consultee 6 Edwards Lifesciences	1.3 What information is needed	These details are all captured in the registry	Thank you for your comment. See response to comment 62.
65	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	This statement is misleading. The EAG stated the results "were subject to significant uncertainty but did not exclude the possibility that they reflect the true performance of the TAVI devices." Based on the limited evidence reviewed, a more accurate statement would be 'analyses are too uncertain to determine whether or not the differences in cost between valves are justified.' Despite all of the limitations, looking more in depth at the EAG report and the analysis performed in the base case from the economic evaluation, we clearly see an outlier, statistically significant) with the highest NMB - which is SAPIEN 3 for both male and female patients(page 62 of the Committee Papers)	Thank you for your comment. The committee's conclusions were based on both publicly available and confidential evidence discussed in part 1 and part 2 of the committee meetings, respectively. While Sapien 3 had the highest probability of highest net monetary benefit, the estimates of net monetary benefit could not be shown publicly due to confidential pricing agreements. The net monetary benefit confidence intervals overlapped

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			There is strong published evidence demonstrating that SAPIEN 3 Ultra is at least as good as SAPIEN 3.	significantly between valves (see section 3.20 of the guidance). Evidence on the comparative performance of Sapien 3 and Sapien 3 Ultra was reviewed by the EAG (see section 5.2 of the assessment report).
66	Consultee 6 Edwards Lifesciences	2.10 Sapien 3 and Sapien 3 Ultra (Edwards)	This is not accurate and LR is missing. Latest IFU (including S3UR) states: 1. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valve system is indicated for use in patients with heart disease due to native calcific aortic stenosis at any or all levels of surgical risk for open heart surgery. 2. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valve system is indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of an aortic transcatheter bioprosthetic or surgical aortic or mitral bioprosthetic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).	Thank you for your comment. The guidance has been amended to ensure factual accuracy.
67	Consultee 6 Edwards Lifesciences	3.19 Cost effectiveness	The confidence intervals for SAPIEN 3 did not overlap. Please change this statement. The differences in NMB are also supported in literature, which has been supplied previously to NICE but has not been considered. It is also important to note that the EAG does not exclude the	Thank you for your comment. See response to comment 65. Evidence on the economic value of Sapien valves was reviewed by the

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			possibility that these results could “reflect the true performance of the TAVI devices”	EAG and considered by the committee (see section 6.1 of the assessment report).
68	Consultee 7 Boston Scientific	1.3 1 Recommendations	We support the recommendation that trusts have access to a range of valves, and that clinicians will continue to have the freedom to choose the most clinically appropriate valve.	Thank you for your comment, it has been noted by the medical technologies advisory committee.
69	Consultee 9 Abbott Medical	1.2 1 Recommendations	Abbott requests that it is made clear whether this "least expensive option" incorporates the value add or not. The least expensive option without the value add may not be the least expensive option when value add is considered.	Thank you for your comment. The committee concluded that it was appropriate to account for ‘added value’ agreements in the valve cost (see section 3.19 of the guidance).
70	Consultee 10 Medtronic	3.14 Relative performance between valve generations	The statement below was made by a Medtronic company representative and we feel that it is important to clarify that she was referring to certain outcomes yet the statement may be interpreted as all outcomes. Therefore we suggest a minor change as follows: “A…. company representatives explained that usually newer generations make incremental improvements and that these are often small changes which would not affect **certain** outcomes, such as durability.”	Thank you for your comment. The wording of the guidance has been amended as suggested.
71	Consultee 12 Heart Valve Voice	1 Recommendations	NICE is uniquely positioned to champion the collection of comprehensive, long-term data on medical devices, especially given the NHS’s centralised capabilities. Unfortunately, the current systems in place for data collection and clinical audits are underfunded and lack the scope required to generate meaningful, real-world evidence on the long-term performance of heart valves. Heart Valve Voice strongly urges NICE to prioritise the development of more robust data collection processes to ensure that future decisions are grounded in solid, real-world evidence. For this	Thank you for your comment. Please see response to comment 51. The committee’s considerations related to further evidence derived from the UK TAVI registry are presented in sections 3.25 and 3.26 of the guidance.

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			to be effective, the data collection must be clinician-led, adequately funded, and supported by modern, efficient systems. This will not only improve patient safety but also ensure that cost-effectiveness decisions are based on reliable evidence.	
72	Consultee 12 Heart Valve Voice	Not specified	As the consultation process continues, Heart Valve Voice encourages NICE to take a cautious, evidence-driven approach in refining its recommendations. Decisions based on incomplete or inadequate evidence can place patients at significant risk, compromising the quality of care they receive. We would also call on NICE to collaborate closely with the MHRA and other relevant bodies to improve data collection, enhance monitoring systems, and ensure that the evidence used to inform decisions is both comprehensive and of the highest quality. While we understand the need for cost-effectiveness within the NHS, patient safety and clinical outcomes must always be the priority. In summary, we believe the current recommendations do not reflect the evidence we and other stakeholders have presented. We hope that as the process moves forward, NICE will carefully reconsider its approach to ensure that patients continue to receive the safest and most effective care possible.	Thank you for your comment. See responses to comments 21, 38 and 51.

Indication and regulation

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73	Consultee 6 Edwards Lifesciences	Not specified	Likewise, guidance recommendations should not be issued for technologies outside of their indication for use, especially when they have not generated evidence to gain specific regulatory approval.	Thank you for your comment. The committee recommended using a transcatheter heart valve that is considered clinically appropriate for the person with aortic stenosis having TAVI. It heard that in rare occasions interventional cardiologists may use valves outside of their intended use when this is considered the most clinically appropriate option (see section 3.4 of the guidance). The decision which valve is clinically appropriate for each person with aortic stenosis who has been selected for TAVI is made by the interventional cardiologist and is expected to include the product's intended use. sections 6.1.11 and 6.1.12 of NICE's health technology evaluation manual specify that 'The committee does not normally make recommendations on using a technology outside the terms of its regulatory approval' and that 'Evidence relating to the technology being evaluated that is outside the terms of its regulatory approval may be considered during the assessment phase of the evaluation'.

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74	Consultee 6 Edwards Lifesciences	1.3 1 Recommendations	This is the only sound recommendation that can be drawn from the evidence presented and clinical expert recommendations. Other evidence has been shown to be highly uncertain yet appears to have been overlooked, whereas this deals well with the recognised uncertainty. It should be clearly noted that not all valves have the licensed indications for all patient categories in this assessment and clinicians should follow Table 2 EAG from a regulatory perspective. Perhaps a form of this table needs to be included in the guidance document.	Thank you for your comment. The committee heard that most people for whom TAVI has been selected as the appropriate treatment option are at high surgical risk. Also, most TAVI procedures are done to replace a native aortic valve. The committee noted that all the valves in the assessment are indicated for this population (see section 3.4 of the guidance).
75	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	Valves also vary by licensed indications and level of supporting data This has been completely overlooked in this draft guidance - despite the work done by the EAG on that topic (Page 8 of the Committee papers document)	Thank you for your comment. The committee acknowledged that valves vary in intended use (see section 3.4 of the guidance). The committee discussed the value of differences in supporting data and concluded that all valves have enough evidence to be used in the NHS, but that the available evidence does not allow for direct comparison between different valves. Please also see response to comment 36.
76	Consultee 6 Edwards Lifesciences	2.3 2 The technologies	Data was unavailable for 5 out of the 11 TAVI devices. The EAG states their outcomes are unknown, so by definition are not included in the assessment. Also, these valves do not have licensed indications for the entire spectrum being considered. It is unsound to generalise across devices and the recommendations need to be revised accordingly.	Thank you for your comment. Please see responses to comments 14, 21, 38, 57 and 73.
77	Consultee 6 Edwards Lifesciences	3.4 Choice of valve	As there is a large degree of variation in licensed indications, specific recommendations by risk categories should have been considered including the C/E evaluation. All valves are licences for HR patients but not all are licensed in patients	Thank you for your comment. The guidance was amended to remove any reference to the cost-effectiveness

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			with lower risk. TAVI devices are found to be highly cost effective in HR patients with an ICER of £7k / QALY with a device cost at £17.5k and this information should be included in support of the expert observation which is supported by the registry data.	of TAVI versus surgical valve replacement.
78	Consultee 6 Edwards Lifesciences	3.4 Choice of valve	The opinion of one clinical expert should not be considered to be authority to use a technology outside of its regulatory approval in this or any other NICE guidance. One opinion is very much at the lowest end of hierarchy of evidence. By inserting this comment by one clinical expert in a guidance document. It also suggests that NICE is endorsing the use of medical devices outside of their indications for use.	Thank you for your comment. Please see response to comment 73.
79	Consultee 6 Edwards Lifesciences	3.12 Evidence for valves not captured in the UK TAVI registry	If there is no data for these valves, then no guidance should be issued on them. It is unfair to the companies involved and potentially dangerous for patients to receive recommendations on technologies based on no evidence.	Thank you for your comment. Please see responses to comments 14, 21, 38 and 57.

Previous generations

Comment number	Name	Section number	Comment	Response
80	Consultee 2 British Cardiovascular Intervention Society	Not specified	[redacted] commenting on behalf of the British Cardiovascular Intervention Society (BCIS) With respect to the Draft guidance document, BCIS has the following comments:- 1. The guidance concludes that there was no evidence of a difference between TAVI valves identified by this consultation. It therefore concludes that there is no reason to distinguish between the valves, and therefore the cheapest valve should be used by default. This is an inappropriate conclusion. The LSA process did not look at the appropriate data to assess the 11 different valves. This is why no difference was identified, not because there is no difference. We will expand on this below. 2. The LSA should have looked more broadly at the totality of evidence/data for each valve type. Two of the valve types (Edwards SAPIEN and Medtronic Evolut), have vastly more data to support their safety and efficacy. They have multiple RCTs in many thousands of patients, with follow-up in multiple RCTs up to 5 years. They have registry data including long-term follow-up to 10 years. None of the other valve types has anything like this amount of data. Several have none or almost none from RCTs. 2. The LSA should have considered long-term outcome data with the different valves assessed. Edwards SAPIEN and Medtronic Evolut have RCT data to 5 years, and registry data to 10 years. None of the other valves has 5 year data.	Thank you for your comment. The EAG acknowledged in the assessment report that “Longitudinal evidence is only available on earlier generation devices where poorer outcomes are expected. Newer device models typically phase out earlier models, however device sizes may vary between models and therefore the populations in which different generations of valves are used cannot be assumed to be exactly equivalent.” The longest available follow-up for the devices listed in the Final Scope, and for the device family where multiple generations of a device were available from a manufacturer, were summarised in Table 37 of the assessment report and considered by the committee. Because the purpose of the LSA is to inform future procurement decisions, evidence relating to older generations of valves will become even less relevant as time goes on. The totality of UK real-world evidence for each valve is provided in section 5.3 of the assessment report and has similar relative availability by valve to the clinical evidence. In multivariate analysis, this is reflected in the width of the confidence intervals for the valve-

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			3. The LSA should have considered the totality of global and UK experience with the different valves. Edwards SAPIEN and Medtronic CoreValve/Evolut have been used in the UK for 17 years and in 10s of thousands of patients. None of the other valves has anywhere near this degree of experience globally or in the UK. 4. Considering the above we do not believe it is reasonable to conclude that there is no difference between the TAVI valves, and the cheapest should be used where possible. We believe that those valve types with vastly more data, much longer term follow-up data, and far greater experience globally and in the UK, can be distinguished from the other valve types	specific covariates for each outcome measure. Please also see responses to comments 14, 19, 21 and 38. The committee recalled that clinicians and patients value the availability of long-term data, but that it is often less relevant because of differences in the population, clinical pathway and transcatheter heart valves themselves, so it concluded that the availability of long-term data for a valve family does not justify a higher price for current iterations (see sections 3.15 and 3.23 of the guidance).
81	Consultee 6 Edwards Lifesciences	1.3 Why the committee made these recommendations	This definition of the assessment is different to the main summary because the only way that “differences in clinical, economic and non-clinical outcomes between the different valves” can be “attributed to innovative features or characteristics of the valves” is by comparing them to previous generations of that valve and not against other valves. It’s impossible otherwise to draw any conclusions as to why there are clinical differences. To look at a two-year window of data from the TAVI registry is not going to capture any inter- or intra- valve differences adequately, as shown in the EAG report and in the expert comments. Non-clinical outcomes have been overlooked. From the UK TAVI registry and the EAG report (Table 17), we observe some statistical differences in important outcomes such as the procedure time and length of stay between the TAVI valves that are not captured in this draft guidance.	Thank you for your comment. Non-clinical outcomes were collected through the user preference assessment, which represents a systematic process for identifying and quantifying their importance. The process concluded that most of the reasoning for choosing a specific valve is based on clinical factors and outcomes, so price differences could not be justified by other non-clinical factors (see section 3.24 in the guidance and the user preference report). Please also see responses to comments 15 and 22.

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			These are just a few examples of why this guidance is not based on a robust assessment of all relevant evidence.	
82	Consultee 6 Edwards Lifesciences	3.14 Relative performance between valve generations	The reported comment by company representatives does not make any sense. There is no reason to make an incremental innovation if it is not intended to improve outcomes. This comment should be removed. The evidence that was asked for by the EAG included the following question: "How does your technology differ from other technologies in the category? Please give details in terms of how the differences affect clinical and non-clinical outcomes." The data supplied in response to this question would show how the improvements in the devices lead to improvements in outcomes. Once again, this guidance is not issued on evidence and "likely" indicates that EAG is basing the relative performance report on anecdote, not on evidence. Until relative performances are assessed based on available robust data, no assumptions should be made.	Thank you for your comment. The committee heard from a specialist committee member and company representatives who explained that usually newer generations make incremental improvements and that these are often small changes that may not affect certain outcomes, such as durability (see section 3.14 of the guidance). The EAG highlighted that clinical studies between generations typically have short follow up and do not provide long-term data, with the longest follow up being 1 year – evidence identified comparing valve generations is summarised in section 5.2 of the assessment report.
83	Consultee 10 Medtronic	3.14 Relative performance between valve generations	We agree with the following statement from section 3.14 and therefore feel it is important that procurement bodies are aware of the similarities between valve iterations as well as the differences: "**it should not be assumed that a newer valve is non-inferior if the differences between valves are substantial (for example, changes in the leaflet tissue)".** For the Medtronic TAVI valves, there have been no changes made to the valve leaflets themselves and therefore we ask that the following statement is added to the product description for Evolut valves in section 2.6: **"No changes have been made to the valve housing or leaflets as the design has progressed from Evolut R through Evolut FX."**	Thank you for your comment. The wording of the respective sections has been amended as suggested.

Confounding factors

Comment number	Name	Section number	Comment	Response
84	Consultee 6 Edwards Lifesciences	1.3 What information is needed	While both of these are missing from the RWE in the TAVI registry, the guidance does not explain in what way these factors make a clinical difference, and if so, the magnitude of that difference: Two references that should have been used to inform this conclusion are: • Guimarães et al. International Journal of Cardiology, Volume 306,2020, 20-24 multicenter (n=626): No association between high index calcium score and 30-day mortality and stroke for SAPIEN 3. This study classified high and low scores based on the median value for each sex. • Larroche et al. Int J Cardiovasc Imaging. 2020 Apr;36(4):731-740, single center (n=352): assessing the impact of Aortic valvular calcium score (AVCS) on clinical outcome (Device Success (DS), Major Adverse Cardiac Event (MACE) and PVL) for both BEV and SEV. "the relationship between AVCS and TAVR results seems to be more complex, with a U-shaped curve, where a low calcification rate leads to a risk of embolisation and excessive calcification leads to a risk of misdeployment or para valvular regurgitation. So, there seems to be a middle way to be found and measuring the calcium score when preparing a TAVR could be a simple tool to add to the usual visual assessment. Moreover, the results suggest that a high AVCS particularly affects the DS when it involves auto-expanding valves and when the distribution of valvular calcium is symmetric. These two points could be related to a misdeployment of the prosthesis, in the case of local calcium amalgams, which could lead to the occurrence of leak or obstruction. Indeed, self-expanding valves adhering to existing anatomy while balloon-expandable valves forcing their circular expansion through radial force".	Thank you for your comment. The committee heard that that the anatomy of the valve being replaced and the level and distribution of calcium are particularly important when choosing a valve and can be strong predictors of clinical outcomes (see section 3.3 in the guidance). The committee also heard that recording of calcification is complex and that calcium score does not capture all relevant information. UK TAVI registry representatives stated that they are working with NHS England and commissioned hospitals to improve data collection, and that they are engaged with the Medical Device Outcome Registry, to facilitate the generation of information about device-specific outcomes. The wording of section 1 of the guidance has been amended to provide clarity on the role of valve calcification in future research.

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			This data suggests that distribution of calcium around the valve is more problematic for self-expandable valves than balloon-expandable valves. This relative effectiveness aspect has not been explored at all in the guidance.	
85	Consultee 6 Edwards Lifesciences	3.3 Choice of valve	Using the level of calcium as a predictor of outcome for all valves is not supported by literature Guimarães et al 2020, multicenter (n=626): No association between high index calcium score and 30-day mortality and stroke for SAPIEN 3. This study classified high and low scores based on the median value for each sex. Larroche 2020 single center (n=352) - assessing the impact of Aortic valvular calcium score (AVCS) on clinical outcome (Device Success (DS), Major Adverse Cardiac Event (MACE) and PVL) for both BEV and SEV.	Thank you for your comment. Please see response to comment 84.
86	Consultee 6 Edwards Lifesciences	3.3 Choice of valve	There is a contradiction in this statement in relation to the evidence assessed. On one hand the EAG states that missing components (anatomy and calcium) might explain the differences observed from the TAVI registry and on the other, they state that the majority (50%+) could actually be treated with any TAVI device. If that's the case then the observed differences in clinical outcomes (focusing on short-term were more reliable) should be considered as valid as they are also aligned with the literature [Senguttuvan et al., meta-analysis for example] and the registry data should serve as a reliable source of evidence	Thank you for your comment. The EAG identified several confounders as seen in the published literature or based on Clinical Expert feedback (see section 5.3.1 of the assessment report). The committee heard from experts that most people with aortic stenosis (that is, more than 50%) would not need a specific transcatheter heart valve and a wide range could be used (see section 3.3 of the guidance). However, in some cases due to specific characteristics such as valve anatomy or calcification, a specific valve would need to be used. Since these characteristics were not captured it was not possible to determine whether the differences are

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				seen because some valves are only used in specific cases where risk of poor clinical outcomes is higher, or if there are truly differences due to the design of the valve.
87	Consultee 6 Edwards Lifesciences	3.15 Economic model structure	There is no perfect economic model - reason why PSA and DSA were considered. Despite all limitations and uncertainties, some clinical differences are observed from the UK TAVI registry which are aligned with the findings from the literature (RCTs and meta-analysis) - including the Heathcote et al. 2023 publication. From the base case results in the EAG report, we clearly see a device with the highest probability of NMB.	Thank you for your comment. Please see response to comment 65.

Added-value agreements

Comment number	Name	Section number	Comment	Response
88	Consultee 1	1.3 What information is needed	We do not agree with the statement on 'Added Value' agreements between companies and NHS Supply Chain. None of these agreements result in cost returning to NHS England, it is retained by the NHS Trust. Only one of these agreements allows for part of the cost of a valve to be returned to an NHS trust to be spent on structural heart-related items. The others are linked to the purchase of other products in the company portfolio and are spent on a variety of items, that may not be structural heart-related. We consider that such agreements, that are volume related, skews the market and are anti-competitive, preventing uptake of newer TAVI valves. This limits choice for the clinicians and patients and runs counter to two of the NICE recommendations. We would like to see TAVI moved from the Specialised Services Devices Programme (SSDP) to the National Tariff. This would	Thank you for your comment. The wording of this section has been verified by the SSDP and reflects current arrangements. The committee has considered this comment and this is reflected in section 3.19 of the guidance. Please also see response to comment 51.

Comment number	Name	Section number	Comment	Response
			allow for wider commissioning of transcatheter mitral technologies and the commissioning of transcatheter tricuspid technologies. This would also negate the need for 'Added Value' programmes.	
89	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This paragraph on added value agreements is not a true or fair assessment of reality. It is also misleading. Without the added value agreements, NHS resources would be further stretched	Thank you for your comment. The wording of the respective section has been amended to improve accuracy and clarity in consultation with the SSDP.
90	Consultee 6 Edwards Lifesciences	1.3 What information is needed	This sentence is purely speculative and is not based on anything that has been presented to the committee. It should be removed as it has no basis in any evidence that has been presented to the committee	Thank you for your comment. Please see response to comment 89.
91	Consultee 6 Edwards Lifesciences	3.18 Model cost inputs	Edwards does not believe this statement [It also noted that the resources returned through 'added value' agreements can only be spent on structural heart-related products or services at the NHS trust level.] to be true. Please substantiate this comment or remove it.	Thank you for your comment. Please see response to comment 89.
92	Consultee 7 Boston Scientific	1.3 What information is needed	3. We question the statement that added value agreements "will not be resource-releasing for the NHS". The purchases made with the cash released from these agreements are deemed necessary by the hospital, and therefore are likely to have been made/required regardless of the presence of an added value agreement. We request this wording is therefore removed.	Thank you for your comment. Please see response to comment 89.
93	Consultee 9 Abbott Medical	1.3 What information is needed	Abbott do not agree with this statement and request that it is removed. Abbott's TAVI Value Model provides Trusts with access to such a broad catalogue of options that it is absolutely possible to achieve 'resource-releasing' impact from this 'Added value'.	Thank you for your comment. Please see response to comment 89.

Comment number	Name	Section number	Comment	Response
94	Consultee 10 Medtronic	1.3 What information is needed	[redacted]	Thank you for your comment, it has been considered by the medical technologies advisory committee.
95	Consultee 11 Meril UK	3.18 Model cost inputs	3.18 above is not compliant in public procurement law.	Thank you for your comment. The consultee's statement was not confirmed by procurement and commissioning experts approached by NICE.
96	Consultee 11 Meril UK	Not specified	• What is permitted in terms of good and services, to what value vs. volume of TAVI ordered? • Use an RFI to explore what the monies are being used for at each centre.	Thank you for your comment, they have been considered by NICE and the medical technologies advisory committee. The added value agreements are confidential between manufacturers and NHS Supply chain, and so details cannot be shared publicly.

Equality issues

Comment number	Name	Section number	Comment	Response
97	Consultee 1	1.3 What information is needed	We would suggest that amongst the recommended confounding factors in the UK TAVI Registry it should include ethnicity as part of both a clinical and a group of equality factors.	Thank you for your comment. The committee heard that there are inequalities in access to TAVI related to ethnicity and socioeconomic status. It concluded that ethnicity should be recorded and adjusted for in future research.

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98	Consultee 6 Edwards Lifesciences	Not specified	There is also clear evidence that there is inequity of TAVI availability. Patients of a female gender, black or South Asian ethnicities and high deprivation are associated with significantly reduced odds of receiving AVR in England. Although inequalities are identified in the scope, NICE has not demonstrated any consideration of how this guidance could improve these factors in its recommendations or assessment.	Thank you for your comment. During the first committee meeting the committee heard that there are gender and geographical inequalities in access to structural heart services. During the second committee meeting the committee also heard that there are inequalities related to ethnicity and socioeconomic status. The committee concluded that guidance on the choice of valve would not impact access to care, as the decision is made after TAVI has been established as a possible treatment option. This has been reflected in section 3.28 of the guidance.
99	Consultee 6 Edwards Lifesciences	3.25 Equality considerations	There is also clear evidence that there is inequity of TAVI availability. Patients of a female gender, black or South Asian ethnicities and high deprivation are associated with significantly reduced odds of receiving AVR in England. (Rice et al. Open Heart 2023;10:e002373.) Although identified in the scope, NICE has not demonstrated any consideration of these factors in its recommendations or assessment.	Thank you for your comment. Please see response to comment 98.
100	Consultee 10 Medtronic	3.25 Equality considerations	Section 3.25 states the following: “Transcatheter heart valves are available in different size ranges, which may affect whether they can be used in people with different body sizes **(for example, men are more likely to have a large aortic annulus and need a larger valve).”** The scoping equality impact assessment for this LSA topic states that women “experience greater 5- year mortality after diagnosis of severe AS” than men. Additionally, the EAR identified evidence that revealed significant differences in timely AVR based on sex (Rice et al. 2023). The NICOR 2024 report for the UK TAVI registry states ‘there may be an under-	Thank you for your comment. The wording of the respective section of the guidance has been amended.

Comment number	Name	Section number	Comment	Response
			provision of TAVI treatment to female patients.' The EAR also stated that "The Clinical Experts also advised that while many patients can be treated with any TAVI device, there are some subgroups, such as those with a small annulus, who may be better suited to a particular device for its specific features, such as expansion type or intra- or supra-annular leaflets" Given that women are the underserved population regarding sex differences in access to TAVI, we recommend that the statement in section 3.25 is updated as follows: 'Transcatheter heart valves are available with **different design features** and in different size ranges, which may affect whether they can be used in people with different body sizes (**for example, women are more likely to have a small aortic annulus and need a smaller valve)'**	

User preference assessment

Comment number	Name	Section number	Comment	Response
101	Consultee 6 Edwards Lifesciences	3.22 Justification for price variation	User preference analysis was included, but this was based on the opinion of very few clinicians and was not opened to a wider care team input. The limited sample size and narrow field of expertise surveyed indicated that the methods for establishing user preference methods were poor.	Thank you for your comment. NICE's interim process and methods statement for late-stage assessment states that "The aim of capturing user preferences is to transparently collect and present information to the committee on the criteria that users consider important when deciding which technology to choose. Users are defined as those who will use the technology and are directly involved

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				in the decision to choose one technology over another." NICE identified interventional cardiologists as the relevant user for the user preference assessment. A number of interventional cardiologists were invited directly or through institutional representatives to participate at all stages of the user preference assessment.
102	Consultee 7 Boston Scientific	3.22 Justification for price variation	When mentioning the User Preference Assessment, it should be clearer that this was a methodology not previously conducted by NICE before, and should be seen as evolving. It had several limitations, including but not limited to, its sample size.	Thank you for your comment, it has been considered by the medical technologies advisory committee. Stakeholder concerns about the sample size have been reflected in section 3.24 of the guidance. NICE acknowledges that it is a new process but this fact was not relevant to the committee's decision making.

Resource impact

Comment number	Name	Section number	Comment	Response
103	Consultee 6 Edwards Lifesciences	3.20 Resource impact	It is unclear why the committee were asked to consider this hypothetical, misleading scenario rather than a scenario that is more realistic, supported by literature and within the licensed indications of all technologies concerned Only HR should be considered as this is a common indication across devices and also where there is convergence between the EAG findings and the literature on the better performance of specific devices. What is more concerning is that the focus is on price and not on value for money – the committee should be	Thank you for your comment. Section 4.38 of NICE's interim process and methods statement for late-stage assessment states that "The committee can consider budget impact analyses when exploring the level of decision-making uncertainty associated with the technologies being assessed."

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			asked to consider a scenario where the most cost-effective valves were used in order to achieve the LSA goal to “maximise clinical effectiveness and value for money.”	The resource impact assessment conducted for this late-stage assessment aimed to show the direction of change if there was to be a market shift when accounting for device costs and added-value agreements. The modelled shift was considered appropriate by the committee. As most people currently having TAVI are at high surgical risk, the scenario does not present a possible shift that would require valves to be used outside their licensed indications (see section 3.4 in the guidance). Since the committee concluded that the evidence was not sufficient to determine whether there were differences in cost-effectiveness between available valves, the resource impact assessment focused on price only.
104	Consultee 7 Boston Scientific	3.20 Resource impact	We require more information around the statement that a 10% shift to less expensive valves could fund additional TAVI procedures if reinvested into the service. A 10% shift could also fund various other non-cardiac initiatives, and indeed could end up plugging inefficiencies in the system elsewhere, with benefits not recognised by TAVI practitioners or heart valve disease patients. If this statement is to be made, we request a commitment to a plan where savings made would be reinvested into alleviating the specific blocks that currently exist in the TAVI pathway, given that the UK is far behind its European neighbours in this area.	Thank you for your comment. The respective section of the guidance was amended to state that a shift could result in net cost savings for the system.

Process

Comment number	Name	Section number	Comment	Response
105	Consultee 4	4 Specialist committee members	Can you explain or otherwise justify the presence of 4 cardiac surgeons in a piece of work on TAVI? Only 3 TAVI cardiologists	Thank you for your comment. Interventional cardiologists were recognised as key stakeholders from the beginning of this assessment. NICE liaised with both individual experts and institutions (including the British Cardiovascular Intervention Society, Royal College of Physicians, British Society for Heart Failure, and the British Cardiovascular Society). Individual experts were invited to act as expert advisers and to apply to serve as specialist committee members. Institutions were invited to register as stakeholders and to circulate the call for expert advisers and specialist committee members. Three interventional cardiologists were recruited and joined the medical technologies advisory committee for this late-stage assessment. Cardiac surgeons were included as part of the multidisciplinary heart team involved in the care of people with aortic stenosis. All of NICE's programmes adhere to a rigorous process to ensure compliance with the NICE conflict of interest policy, which is designed to uphold the highest standards of transparency and integrity. In all instances, across all NICE

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				committees, a direct financial conflict of interest will preclude healthcare professionals from making recommendations on a particular topic and this has resulted to some interventional cardiologists participating at committee as experts and not specialist committee members. From the outset, we have recognised the importance of including experienced TAVI operators on the committee and fully value their expertise. Throughout the process, we had a number of interventional cardiologists contributing, some in their capacity of experts and others as committee members. Due to stakeholder concern about the makeup of the specialist committee, 6 interventional cardiologists were also invited to serve as expert advisers, and participated in the committee meetings for this late-stage assessment. Expert advisers were able to see and comment on the confidential evidence for this late-stage assessment in order to maximise their contribution. Both individual and institutional representatives of the interventional cardiologist community were able to comment during public consultation on the draft guidance.

Comment number	Name	Section number	Comment	Response
				Interventional cardiologists were identified as the relevant user of transcatheter heart valves and participated in all stages of the user preference assessment for this assessment.
106	Consultee 4	4 Clinical experts	I can see that I have been omitted from this list.	Thank you for your comment. The list of experts in the guidance only includes those who attended committee meetings. Those who contributed to the assessment report or the user preference report are acknowledged in those documents.
107	Consultee 6 Edwards Lifesciences	Not specified	Edwards Lifesciences has participated in and contributed to numerous HTA's both in the UK and globally. We are astounded that NICE has produced guidance using such fundamentally flawed and unfair processes, methods and reasoning, which are clearly evident in this LSA. The choice to repeatedly ignore the majority of stakeholder input and the choice to ignore the overwhelming majority of evidence and information to help to answer the decision problem demonstrates that NICE has not taken an evidence based approach. It is consequently likely to have the opposite of the desired effect of improving quality and value and sets the NHS back many years in its approach to decision making. NICE has exceeded its powers in ignoring the regulatory processes in reaching its unsound conclusions and in not following the standard hierarchy of evidence approach in HTA, going as far as recommending (by default) technologies which are not licensed in a particular indication and/or for which the clinical and economic data are "unknown".	Thank you for your comment. This assessment was conducted in line with NICE's interim process and methods statement for late-stage assessment and NICE's health technology evaluation manual. Please note that NICE considers all types of evidence in its evaluations. This includes evidence from published and unpublished data, data from non-UK sources, databases of ongoing clinical trials, end-to-end studies, conference proceedings, and data from registries, real-world evidence and other observational sources. The preferred source of evidence depends on the specific use being considered. Section 3.3.6 of NICE's health technology evaluation manual specifies that the relevance of RCT evidence to

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			Edwards supports the principle behind the introduction of LSA. Throughout this LSA, we have tried our utmost to help NICE produce sound guidance. What NICE could, and should, have done to produce useful guidance is to firstly examine the use of different TAVI devices in high risk (HR) surgical candidates. This is the only indication common to all devices. The analyses for high risk surgical candidates should have then been separated by different expansion types. Low (LR) and intermediate risk (IR) should have been modelled separately where indications for the individual devices permit. This would reflect the output of the regulatory processes for the development of medical technologies.	the evaluation depends on both the internal and external validity of each trial. Internal validity is assessed according to the design, analysis and conduct of a trial. It includes blinding (when appropriate; this is often not possible when trials use specific medical devices or diagnostics), the method of randomisation and concealment of allocation, and the completeness of follow up. Other important considerations are the size and power of the trial, the selection and measurement of outcomes and analysis by intention to treat. External validity is assessed according to the generalisability of the trial evidence, that is, whether the results apply to wider patient groups and to routine clinical practice. In the assessment report the EAG has provided a rationale that outlines its assessment of the validity for existing RCTs. Please see also response to comment 29 for the inclusion of additional RCTs and meta-analyses. Stakeholder input has been listened to and acted upon at multiple stages, through consultations on the scope, the interim methods and process statement, the assessment report and draft guidance. Regarding surgical risk please see response to comment 25. Regarding

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				how this applies to regulatory approval please see response to comment 73.
108	Consultee 6 Edwards Lifesciences	Not specified	In this particular LSA, there has been significant deviation from anything in the NICE procedure manuals and even from either version of the belatedly issued Interim Methods and Process. One example of this (among many others previously communicated to NICE) is that the measurement and criteria for justifying price differences does not exist in any NICE manual – there is no clear description in the methods of what benefits are expected, or threshold of clinical superiority which drive a justifiable price difference. Please explain against what standards were objective measurements of price difference made in this assessment?	Thank you for your comment. Section 4.17 of NICE's interim process and methods statement on late-stage assessment states that the willingness-to-pay threshold for clinical benefit of one device over another remains the NICE reference case of £20,000 per QALY. Sections 4.37 and 4.38 further explain that "The committee considerations include: assessing clinical, user preferences and technical requirements, pricing and NHS budget impact, other potential impacts on the healthcare system, patient and carer views on the condition and experience of using the technology, equality issues, the uncertainty and quality of the evidence" and that "The committee can consider budget impact analyses when exploring the level of decision-making uncertainty associated with the technologies being assessed". For this late-stage assessment the committee considered whether price differences can be justified by high-certainty differences in patient or system outcomes from a range of evidence sources, as well as by other non-clinical outcomes or issues. It concluded that there is not enough

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				evidence to determine whether price variations between different transcatheter heart valves are justified.
109	Consultee 2 British Cardiovascular Intervention Society	Not specified	[redacted] commenting on behalf of the British Cardiovascular Intervention Society (BCIS) BCIS has major reservations over this document, and the processes which led to its development, which we believe to be highly flawed. With respect to the process, we would highlight the following issues:- 1. The process was far too rigid, without application of common sense. This could be attributed to the failure to include appropriate clinical specialists i.e. interventional cardiologists who do TAVI procedures, in the process from the outset. 2. The specialist committee did not include the appropriate specialists. The committee included 5 cardiac surgeons, none of whom does TAVI, and none of whom makes decisions on what TAVI valve to use in a given patient. The specialist committee should have been populated by interventional cardiologists who do TAVI.	Thank you for your comment. See response to comment 105.

NICE's press release

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110	Consultee 2 British Cardiovascular Intervention Society	Not specified	3. We consider it inappropriate that NICE produced a press release based on draft consultation prior to completion of the consultation phase. Furthermore, the tone and content of the press release did not match the actual guidance.	Thank you for your comment. This comment is not related to the guidance. The press release was retracted on 9 October 2024.
111	Consultee 6 Edwards Lifesciences	Not specified	Given that these are draft recommendations, subject to change, please explain why unequivocal, inaccurate representations - strongly saying that this is the final conclusion - of them have appeared in press releases on August 9th (NICE news) and September 2nd (Health Service Journal)	Thank you for your comment. This comment is not related to the guidance. The press release has been retracted on 9 October 2024.

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112	Consultee 10 Medtronic	Not specified	Press Release 9/8/24: We are very concerned regarding the premature and misleading press release that was issued by NICE on 9th August headlining **"No evidence to support the price variation in heart valves used by the NHS. Draft guidance issued today (9 August) states that the variation in price the NHS is paying for valves used in keyhole heart procedures is not supported by reliable evidence"** The statement **"No evidence to support the price variation in heart valves used by the NHS**" suggests that the committee has **determined that there is no difference between valves**, which is not the case. We believe that this summary is factually inaccurate and misrepresents the committee's conclusions as stated below: **• "It was not clear in the clinical evidence whether there are differences in clinical effectiveness between different companies' transcatheter heart valves due to incremental innovations between the valves" [Section 3.13]** **• "Clinical equivalence between companies' valves could not be assumed. [Section 3.13]** **• "The model results were too uncertain to determine whether there were differences in the cost effectiveness of the transcatheter heart valves" [Section 3.19]** **• "It was not possible to determine whether the differences in cost between valves were justified by benefits derived from incremental innovations".** We believe that this headline is factually inaccurate in stating that **"there is no evidence to support the price variation....." and "variation in price is not supported by reliable evidence..."** as the EAG did not conduct a systematic review of	Thank you for your comment. This comment is not related to the guidance. The press release was retracted on 9 October 2024.

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			the substantial body of high-quality published evidence and relied solely on outcomes data from around 30% of patients from the UK TAVI registry for the clinical and economic assessments. This registry data is limited by data availability and completeness and lack of adjustment for confounders and the **committee concluded that the registry data did not capture enough detail to provide reliable estimates of relative efficacy between valves.** Th**e committee also concluded that the bias and limitations of the clinical inputs to the economic model leads to significant bias in the results of the economic model.** The committee's conclusions clearly show that they were **"unable to determine a difference"** and not that "**there is no evidence to support...**." and we ask that a correction is issued for press statement to reflect that the committee was unable to determine a difference due the exclusion of all of the published evidence from the EAG assessment. We ask NICE to ensure that any subsequent press releases accurately reflect the committee conclusions and the wording in the recommendations.	

Comment number	Name	Section number	Comment	Response
113	Consultee 10 Medtronic	Not specified	Press Release 9/8/24:The quote below from Prof Benger is also factually incorrect and misleading as it states “ We have looked for evidence to determine whether differences in innovation and performance between these valves can justify their range in price, but the i**nformation we have seen does not support the current variation in cost”.** From the very limited “information they had seen”, the committee actually concluded that “th**e registry data did not capture enough detail to provide reliable estimates of relative efficacy between valves**”. The “information that was seen” was limited to TAVI registry data and a systematic literature review of the published evidence was not conducted. **The quote from Prof Benger concludes**: “We hope this **evidence-based guidance** will provide commissioners with the confidence to agree a cost-effective price and allow the NHS to reinvest the money saved to treat more patients as a result”. We believe that this statement is also misleading as the guidance is not based on the evidence and the committee actually concluded “T**he model results were too uncertain to determine whether there were differences in the cost effectiveness of the transcatheter heart valves**” [Section 3.19].	Thank you for your comment. This comment is not related to the guidance. The press release was retracted on 9 October 2024.
114	Consultee 10 Medtronic	Not specified	Press Release 9/8/24: We question why a press release was issued at this stage, when the draft guidance is subject to change following consultation.	Thank you for your comment. This comment is not related to the guidance. The press release was retracted on 9 October 2024.