NICE National Institute for Health and Care Excellence

HealthTech Programme

Medical Technologies Advisory Committee (MTAC)

GID-HTE10027 Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis: late-stage assessment – 3rd meeting Thursday 17 July 2025

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Link to SCM list for topic:	specialist-committee-members
Link to Expert list for topic:	expert-advisers

The following documents are made available to the committee:

1. HTE10027 MTAC3 Cover sheet
2. HTE10027 TAVI Resolution panel briefing and outcome [REDACTED]
3. HTE10027 Factual accuracy check stakeholder comments and EAG responses to the 2nd Addendum to the external assessment report (EAR) [noACIC]
4. NG208 TAVI Surveillance report [REDACTED]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis: late-stage assessment

Resolution request from Edwards Lifesciences for panel discussion

Resolution request 1

Submitted in response to the guidance in general and also referenced sections 3.6, 3.7, 3.8, 3.12 and 3.17. Please note that the request covered several different claims, of which many the initial scrutiny panel did not consider to be grounds for resolution. The parts of the request relevant to the panel discussion are reproduced here, with the full text and NICE's response to the part not upheld in Appendix A. The panel is asked to consider whether resolution grounds of breach of process have been met.

Comment text

Fundamentally flawed approach

The process followed in this appraisal fell far short of the standards required of NICE. NICE publishes procedures to ensure appraisals are carried out with necessary rigour and thoroughness, which safeguards the validity of the recommendations NICE makes at the conclusion of an appraisal. In this instance, the whole of the appraisal process lacked direction or a clear framework to guide it, as exemplified by the fact that the appraisal began without any formal methods or process in place.

Even when NICE published an interim methods and process guide for Late Stage Assessments ("LSAs") four months into the TAVI assessment, there remained many instances of a lack of clarity and deviation from NICE's normal methods. Certain key procedural decisions that NICE took departed materially from the established process and contributed to an incomplete and

partially sighted review of the evidence. For example, the draft scope was published immediately ahead of the scoping meeting and there was no formal consultation period, with stakeholders only granted 24 hours to submit comments. Further, there were various examples of deviation from the intended methods throughout the running of the appraisal. As a result, the process itself lacked transparency, and has led to draft guidance which does not respect the licensed indications for the products, nor does it seem to allow NICE to make a particular reference to technologies within the group which have clear evidence to support their cost-effectiveness. Leaving aside that this LSA materially departed from the interim procedure, the LSA process itself was unfit for purpose, and NICE should have instead considered conducting the appraisal through single technology appraisals for each product.

…For reference, we list the key timings in this appraisal below:

Topic selected and “in progress”	17.10.23
Registered as stakeholder	18.10.23
Request for product and clinical information (no prior notification)	10.11.23 (deadline 24.11.23)
Invitation to scoping workshop received (no prior notification of date)	21.11.23 (date of meeting 30.11.23)
Product and clinical information returned	24.11.23
Online meeting with LSA team	29.11.23
Draft scope received	29.11.23
Scoping meeting (informed that there would be no consultation, but we could send a response letter if received by close of business on Dec 1st)	30.11.23
Comments letter (on draft scope) sent	01.12.23
Final scope published	08.12.23

Edwards letter commenting on final scope	Part one: 20.12.23; Part two: 15.01.24

…

Various statements in the guidance are not consistent with NICE following the LSA process. Key evidence consistent with the scope and decision problem for this LSA has been ignored, and the EAG chose not to systematically review evidence that was relevant. It is not sufficient to ignore relevant evidence by putting forward an argument that the TAVI registry was the most relevant, before systematically reviewing all evidence relevant to the decision problem. This approach is illogical.

An appropriate resolution here is to start again, to ensure that the process itself allows individual technologies to be recommended where the evidence allows, if needs be through individual single technology assessment processes.

Comments from NICE team

The company claims that the following breaches of process occurred:

- Assessment began without a formal process.
- There was no consultation on the draft scope.
- The external assessment group (EAG) decided not to conduct a systematic review.

NICE's health technology evaluation manual states that the resolution process is a final quality-assurance step to ensure that NICE acts fairly, follows its own processes, and produces clear, accurate guidance. It is the NICE team's view that, while these events did occur, they did not result in the stakeholder being treated unfairly or in inaccurate guidance being produced. Each of the claims is addressed in the sections below.

Assessment began without a formal process

NICE was asked by the Department of Health and Social Care (DHSC) to evaluate 8 categories of products and consider whether new methods or process would be required for late-stage assessment (LSA) in mid-2023. The evaluations would be looking at classes of technologies that are in wide use in the NHS where there is a high overall spend and variation in pricing between options. This forms part of NICE's commitment to produce useable and useful guidance and part of the DHSC's Medtech strategy.

The aim of LSA was to assess whether the variation in price was justified by considering the clinical and cost-effectiveness, as well as non-clinical factors, associated with the available technologies. Real world evidence (RWE) was prioritised where appropriate – as the technologies of interest are in wide use it was expected that there would be highly relevant NHS data available to inform the assessment.

While LSA was a new type of assessment, processes and methods were based on those used for established guidance products within Healthtech such as diagnostics guidance and early value assessment (EVA). Elements that would be unique to LSA were developed using a 'test and learn' approach in pilot assessments, similar to the development of other programmes in NICE such as EVA and the proportionate approach to technology appraisals. TAVI was selected as the first pilot as it was an area of high product price variability with a well-established registry.

The TAVI assessment was launched in October 2023 following a period of internal work and consultation with experts and the decision support unit (DSU) to develop interim processes and methods. The initial intention was to complete 8 pilots under a published interim methods and process statement, and then consult on the final methods and process which would be informed by learnings from the pilot assessments. However, due to requests from LSA stakeholders, including Edwards Lifesciences and the Association of British HealthTech Industries (ABHI), it was agreed that consultation would take place on the interim statement as well. Work on the external assessment

report for TAVI was paused while this consultation took place (29th February to 28th March 2024).

Following the publication of the updated interim methods and process statement in April 2024, work resumed on the assessment report which was completed in line with these methods.

The company suggests that doing individual single technology assessments would be a suitable resolution for this LSA. LSA is fundamentally a direct comparison of different available technologies and therefore could only be done as a multi-technology assessment. As part of NICE's transformation of the Healthtech programme to adopt a lifecycle approach, all Healthtech evaluations now assess multiple technologies.

Consultation on scope

The scoping workshop process and micro-timelines for this topic followed established process in the HealthTech Programme and within the variability allowed by NICE's HTA manual. Section 2.5.6 of NICE's HTA manual states that "For diagnostics evaluations, NICE normally holds a scoping workshop and does not have a consultation on the draft scope." The scoping workshop represents the most comprehensive process to understand the decision problem and reach consensus among stakeholders and is usually held instead of consultation.

All companies were given the opportunity to raise their views about the scope during the scoping workshop discussion. Although no consultation on the scope for this assessment took place, stakeholders were given the opportunity to comment on the draft scope by email after the workshop to ensure all relevant points had been considered, as outlined in the resolution request. NICE also provided Edwards Lifesciences the opportunity to submit additional comments after the publication of the final scope on 8th December 2023. Edwards Lifesciences submitted comments to NICE which the NICE team considered and responded to in writing on 18th January 2024.

The LSA interim methods and processes statement, which was consulted on by stakeholders including Edwards Lifesciences, states, "Changes to the scoping process for LSA [from NICE's HTA manual] include… Consultation on the scope will take 7 days and will be followed by a scoping workshop." This was published after scoping for the TAVI assessment had concluded.

No systematic review of evidence

Section 3.3.4 of NICE's HTA manual states "Whatever the sources of evidence available on a particular technology and patient group, a systematic review of the relevant evidence relating to a technology should be done using a pre-defined protocol." However, guidance production in Healthtech has been basing evaluations on pragmatic searches for some time for both interventional procedures guidance (see the IP manual section 9) and early value assessment (see the EVA interim statement section 3.13). These approaches were adapted for the LSA interim methods and process statement, which says that "The evidence reviews may be done using pragmatic approaches when appropriate." As the external assessment report had not been completed at the time this was published, and work on it was paused during consultation on the interim statement, the NICE team considers that the LSA interim statement supersedes the HTA manual.

The EAG's rationale for not carrying out a systematic search of the published evidence was outlined in its protocol, and was agreed with NICE. To summarise, the EAG initially adapted the search strategy used in NG208 to identify systematic reviews of clinical and cost effectiveness and economic models that had been published since the original searches were run. They did not identify any systematic review or meta-analysis directly relevant to the decision problem. Previous consultation comments on the model used for development of the NICE guideline on heart valve disease highlighted that the populations of randomised controlled trials were not representative of a UK NHS population, and therefore may not be relevant to the NHS. The EAG also considered that the assumption of transitivity did not hold (which is required for network meta-analysis), as clinical advice was that the choice of valve

depended on the characteristics of the individual patient – therefore the population of one trial could not be assumed to be eligible for another.

The EAG therefore took a pragmatic, hierarchical approach to the evidence (supported by NICE). RWE from the UK TAVI registry was prioritised as it would be the most applicable to current UK clinical practice. This approach was recognised by the NICE team as a key issue and was highlighted to the committee. The committee reached a consensus position that the RWE was the best available evidence for this assessment (see section 3.10 in the guidance). The EAG also considered published evidence where data in the registry was not available. This was identified using targeted searches, but was supplemented by a large amount of additional evidence identified through stakeholder engagement by NICE, to ensure that no relevant evidence was missed. In particular, stakeholders were encouraged to submit evidence that they felt was relevant to the decision question at the following stages:

- Request for information to companies during the assessment
- Consultation on the assessment report
- Public consultation on the draft guidance.

To address points raised at consultation on the assessment report, the EAG included more detail on available network meta-analyses to provide additional context, describing results and limitations.

Due to the volume of evidence submitted at consultation on the draft guidance, NICE extended timelines to allow the EAG to review the submitted evidence and produce an addendum to the assessment report. This was made available to the committee before the second meeting. Of the submitted papers, the EAG only considered 2 to be key evidence. Having reviewed the submitted evidence, the committee did not change its conclusions from the first meeting.

Initial scrutiny decision

Grounds for resolution referred to panel on potential breach of process only.

Response from Edwards Lifesciences

We are grateful for NICE's resolution panel briefing and the opportunity to provide our comments. However, we wish to raise several issues with the comments from the NICE team.

By law, a technology appraisal must follow NICE's published methods and processes.[1] As NICE itself admits, the Institute breached its processes in multiple instances in this LSA, which undermines the purpose and legal effect of the assessment, and the validity of the conclusions reached.

Further, contrary to NICE's suggestion that the breaches of process in this LSA "*did not result in the stakeholder being treated unfairly or in inaccurate guidance being produced*," it is clear that they have led to (i) the committee and the EAG applying a less rigorous standard and methodology of review than is required under NICE's procedures, (ii) a related lack of transparency, and (iii) a correspondingly flawed outcome (as we set out in our Resolution Comments document (20 Dec 2024) and detail below).

An appropriate resolution would be to withdraw this LSA and undertake a full clinical and cost effectiveness evaluation, with a comprehensive systematic review incorporating all available evidence and a full incremental cost effectiveness analysis, in order to appropriately address the decision problem. In the alternative, we request that recommendation 1.2 "*there is not enough evidence to determine whether price variations between different transcatheter heart valves are justified*" be removed, given that NICE has failed to adequately consider key relevant evidence.

Assessment began without a formal process

NICE's response does not properly address the key resolution point that the Institute began an evaluation without a process in place. Edwards has been, and remains, supportive of NICE's efforts to carry out proportionate and efficient

[1] National Institute for Health and Care Excellence (Constitution and Functions) and health and Social Care Information Centre (Functions) Regulations 2013, Regulation 2.

technology appraisals. In our view, this flexibility contributes to NICE being a world-leader in its field. Nonetheless, there is a marked difference between a welcome degree of pragmatism within the safeguards of an established process and devising an entirely new process in an opaque manner, whose parameters evolve as the review proceeds, and where the output falls far short of requisite standards, as occurred in this instance. The “test and learn” approach and the

fact this LSA was considered by NICE to be a pilot under an undefined interim process does not absolve NICE of the obligation to clearly establish and articulate to stakeholders what process is being used for a specific evaluation. To do anything else is procedurally unfair and exposes patients and physicians to risk.

Irrespective of whether NICE itself had an idea of the elements of other processes that would be incorporated into this LSA, this was not transparently communicated to stakeholders. As a result, we had no visibility over the direction of the LSA and were left at a significant and unfair disadvantage. One example of this lack of transparency and the confusion caused was the letter from NICE on 18 January 2024 which said ***“While we intend to closely align with the existing CHTE2020 manual, we want to ensure that any deviations are clearly communicated”*** *and a separate* communication stated “***the late stage assessment interim process and methods statement will build on the NICE manual, but may include important changes to any of the sections, so please refer to the manual as a starting point only.***” NICE never provided a clear and detailed definition of the intended output of this LSA and how this would be used for decision making, rendering it impossible to conduct a transparent and fair process, as NICE’s procedures demand.

Proceeding in line with established processes is especially important in an LSA, where there is a particular need to be fair between potentially competing manufacturers and technologies. Being clear as to what the process is and ensuring it is followed properly are key elements of a fairly and rigorously conducted assessment.

This is not merely a formalistic point. NICE's processes contain important procedural rules that safeguard the recommendations NICE issues. Deciding to skip over these safeguards or, indeed, commencing an assessment with no such safeguards in place, fundamentally undermines the output of the assessment.

Consultation on scope

As stated above, in principle, Edwards is supportive of efforts to carry out proportionate and efficient technology appraisals, including a short scoping phase if appropriate. However, where NICE is assessing a new area or using a new methodology (as was the case with this LSA), a proper and robust scoping period is required. Further, this LSA was highly complex, with different indications for use for the differing types of TAVI devices, different type of TAVI valve mechanisms (balloon-expandable vs. self-expandable), and different level of maturity in terms of valve generations among the TAVI devices, which was also reflected in extremely heterogenous distribution of valve usage in the main data considered (UK TAVI registry). Indeed, NICE clearly recognized that this complexity warranted a scoping meeting. Despite this, we were not given an opportunity to properly engage with or comment on the draft scope and importantly there was no opportunity for wider consultation for any stakeholder that was not directly involved in the scoping meeting. Therefore, as with much of this LSA, the process NICE adopted with respect to scoping was illogical.

We received the draft scope the day before the scoping meeting, which rendered the workshop redundant given the stark lack of time for the company to properly review and comment on the draft. The lack of time for adequate consultation on the scope in this LSA also contradicts the LSA interim methods and processes statement, which, as NICE notes, requires a seven-day consultation period prior to the scoping workshop. The fact that NICE only published the LSA interim methods and processes statement after scoping in this LSA does not justify the clear lack of an appropriate consultation period. Rather, this supports our point above that NICE's decision to proceed with this LSA prior to the development of any formal process led to pervasive unfairness and a flawed assessment.

Ultimately, this breach of process resulted in a scope that was unfit for purpose, most notably in comparing eleven TAVI devices with distinctly differing regulatory indications, vastly different levels of maturity, and significant discrepancy in the volume of evidence generated between the devices.
Edwards first raised this issue in October 2023 and repeated it on several subsequent occasions. However, NICE failed to address this issue or provide adequate and transparent reasoning for such failure.

Illogical PICO conclusions

The heterogeneous patient populations (five subgroups for the transfemoral approach alone) associated with the eleven transcatheter heart valves (which differ in licensed indication) were the subject of this assessment. This complex situation provided a wide range of PICOs that could not be combined into one single PICO frame. Edwards raised concerns about this consistently from October 2023 into January 2024.

Further confirmation of this came from a direct email from NICE on 1 February 2024, which included the following request: "*Would you be able to send us your side-by-side comparison grid, illustrating the clinical indication, and evidence grades + ref for each indication versus the comparators, SOC and competing valve where they have confirmed CE marking.* ***Obviously where they do not have reg approval, they should not be considered a comparator, this will be helpful to see simply laid out***" (emphasis added). We provided this on 14 February 2024, and NICE acknowledged receipt.

Although the problem resulting from the scoping was made abundantly clear and acknowledged, nothing was done to address these obvious complexities.

No systematic review of evidence

In its comments, NICE accepts that the decision not to carry out a systematic review of the relevant evidence breaches Section 3.3.4 of NICE's HTA manual. This breach of process cannot be justified by NICE's argument that the LSA

interim methods and processes statement provides for pragmatic evidence review “when appropriate,” as this was not communicated to stakeholders in advance of this LSA (given the lack of formal process prior to its commencement).

Further, NICE’s comment that the LSA interim statement superseded the established and consulted-upon HTA manual in this LSA seems illogical. Justifying decisions that contradict and undermine NICE’s formal procedures on the basis of a hastily assembled interim statement – that NICE had not developed and stakeholders did not even receive until after the LSA had commenced – falls far short of the standards of rigour expected of NICE. NICE has published procedures to ensure appraisals are carried out with necessary transparency and thoroughness. They exist for a good reason. They safeguard the validity of the recommendations NICE makes at the conclusion of an assessment. In this LSA, the key procedural decision not to conduct a systematic review of the evidence departed materially from such procedures and led to an incomplete and partially sighted review of the evidence (as we detail below).

Moreover, our point is not merely that the EAG did not conduct a systematic review, but rather that, whichever manner of evidence review was undertaken, the EAG’s review in this case was incomplete and evidence that was material to the decision problem was not adequately considered. As we noted in our letter of 4 February 2025 responding to NICE’s initial scrutiny (Appendix C), the company – and others – submitted substantial evidence to NICE which considers TAVI fairly, accurately and in large numbers. However, NICE failed to (i) give this relevant evidence adequate consideration, and (ii) provide a transparent explanation for its rejection or (iii) provide rationale as to why it took these decisions when the original NG208 model upon which heavy reliance is placed, shared the same study designs. Stakeholders were given no visibility or opportunity to comment on the External Assessment Report addendum detailing the reasons for the omission of certain evidence (which we only received on request on 30 January 2025).

As also noted in our response to initial scrutiny, the reasoning given in this addendum represents a clear case of double standards with regard to "scientific opinion" on which evidence is relevant, given that the justification for rejecting evidence in many cases also applies to the original NG208 model (on which the committee heavily, and unfairly, relied – please see our comments on Resolution Request 2 below). In any event, NICE's failure to share this material document with stakeholders is also a clear breach of NICE's HTA manual (specifically, Sections 5.8.67 and 5.8.69). In addition, this denied Edwards, or indeed any other stakeholder, the opportunity to provide commentary to the committee as to whether this addendum rectified the evidentiary deficiencies we highlighted throughout this evaluation. This represents serious procedural unfairness (please see Resolution Request 3 below).

In response to NICE's technical comments, we also note the following:

- NICE provides that "*the EAG initially adapted the search strategy used in NG208 to identify systematic reviews of clinical and cost effectiveness and economic models that had been published since the original searches were run*." However, this was done to validate the NG208 model structure only. The EAG and NICE neglected to validate their findings in terms of QALY gained by comparing these with the published literature. Comparing TAVI vs. SAVR, NG208 found only 0.024 QALY gained, which is much lower than that found in published literature (specifically, between 2 and 30 times lower). The failure to conduct any validation of the EAG's findings here falls far below the rigorous standards expected of NICE.

- NICE's comments state that the EAG "*did not identify any systematic literature review or meta-analysis directly relevant to the decision problem*." However, Heathcote et al. (2023) incorporates a systematic literature review of all TAVI cost-effectiveness publications (as set out in our Resolution Request 1) and this was captured in the EAG's report.

Despite this, the committee overlooked the systematic literature review in Heathcote et al. (2023).

- NICE states in its comments that "*previous consultation comments on the model used for development of the NICE guideline on heart valve disease highlighted that the populations of randomised controlled trials were not representative of a UK NHS population, and therefore may not be relevant to the NHS*." These previous consultation comments were submitted to challenge assumptions stemming from NG208 relating to the overall treatment effect of TAVI (vs. SAVR) which was based on seven RCTs, some of which were obsolete as they used first generation valves without the add-on skirt to reduce PVL. In NICE's response to these comments, the Institute clarified that although all available trials were still included in the clinical review, the economic model for NG208 (comparing TAVI vs. SAVR) used only trials on second and third generation valves (SAPIEN XT, SAPIEN 3 and Evolut) to inform relative treatment effects. However, as noted in Resolution Request 2, this illustrates that NG208 is outdated, as interventional cardiologists are currently implanting the fifth generation of the SAPIEN platform (which was not even mentioned in this LSA). With this in mind, only the latest RCTs (PARTNER 3) should have been considered to assess the LR indication. Only two TAVI valves have conducted such trials for LR and have clear LR indications. Many cost-effectiveness models have been published in the EU based on the PARTNER 3 trials and the QALY gained is much higher than the findings from NG208.

- NICE also states that "*the EAG also considered that the assumption of transitivity did not hold (which is required for network meta-analysis), as clinical advice was that the choice of valve depended on the characteristics of the individual patient – therefore the population of one trial could not be assumed to be eligible for another*." If we acknowledge that the amount of calcium could be a factor to consider in the choice of the TAVI valve – which was not captured in the UK TAVI registry – RCTs

comparing devices remove this bias. Two FDA IDE trials (PORTICO IDE and Accurate Neo 2 IDE) compare TAVI valves clinically – with clear differences between the outcomes. These have not been considered in this LSA. Assuming that transitivity does not hold and deprioritizing nonUK studies is unfair, as the symptomatic severe aortic stenosis disease has a homogeneous impact on the patients – whatever his or her nationality or origin. The GLOBE (Global Burden of Disease) study,[2] which tracks cardiovascular diseases including aortic stenosis worldwide, shows that severe aortic stenosis remains a significant cause of morbidity and mortality in both developed and developing countries, highlighting the universality of the disease's impact.

- NICE further notes that "*RWE from the UK TAVI registry was prioritised as it would be the most applicable to current UK clinical practice*." As explained in Resolution Request 1, the UK TAVI registry was not fit for purpose for the decision problem (in this case, making comparisons between valves, which is needed to draw conclusions on price variation). Further, the UK TAVI registry had a clear imbalance in sample size among TAVI devices (including no data at all for five out of the eleven TAVI devices in scope) and differences in regulatory indications. As indicated by others in the comments on the first draft guidance, the sole reliance on linked registry data in preference to published RCTs (which were excluded by the EAG based on risk of bias) is a significant deviation from NICE's HTA manual and the NICE real-world evidence framework, which state RCTs as the preferred study design. In accordance with NICE's HTA manual, the EAG would be expected to consider a network meta-analysis if appropriate matching methods are identified for the indirect treatment comparison of TAVI vs SAVR and/or TAVI vs. other TAVI. Section 3.4.11 of NICE's HTA manual states: "*Indirect comparisons and network meta-analyses. When technologies are being compared that have not been evaluated within a single RCT, data from*

[2] https://pmc.ncbi.nlm.nih.gov/articles/PMC10054046/

a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate." However, the EAG determined that retrospective, unvalidated and incomplete TAVI registry data, combined with HES and ONS, is the best available data for the decision problem because the published evidence comparing TAVI devices is "*subject to bias and limited by short term follow up*."

In this context, NICE's decision not to conduct a systematic evidence review and failure to adequately consider substantial relevant evidence submitted by Edwards undermined NICE's established and robust procedures.

Ultimately, the pervasive lack of consistency, transparency and adherence to established process detailed above and in our Resolution Comments documents (20 Dec 2024) resulted in a fundamentally flawed LSA. We therefore request that this LSA be withdrawn and, if still considered necessary, redone, with a comprehensive systematic review incorporating all available evidence and a full incremental cost effectiveness analysis, in order to appropriately address the decision problem. In the alternative, we request that the recommendation 1.2 "*there is not enough evidence to determine whether price variations between different transcatheter heart valves are justified*" be removed.

Panel response to resolution request 1

Ground 1: not met

The panel heard evidence that the LSA began prior to the publication of formal methods or processes, however the topic was paused to allow for input from stakeholders to the interim methods and process statement consultation and that changes were made for the assessment following consultation. However, the panel recognised that this was the first topic addressed through a new form of guidance for NICE, and that the methods and processes used were based on other areas of the HealthTech Programme. In addition, the panel noted that changes were made in response to feedback from stakeholders. The panel heard that there was no consultation on the scope of the guidance, however this would also be the case in the diagnostics programme, and stakeholders were given an opportunity to comment during the scoping workshop and subsequently. The panel noted that the issues raised regarding methods and processes were attributable to the fact that this LSA was the first of a new type of guidance, and concluded that these issues, including those related to scoping, had not fundamentally compromised the integrity of the final guidance.

The panel also heard concerns regarding the selection of evidence, with the suggestion that there has been over-reliance on the TAVI registry and exclusion of other relevant data. It was noted that a pragmatic rather than systematic approach had been taken to evidence searches due to time constraints. However, pragmatic searches are used in the HealthTech Programme, and are not in themselves fundamentally flawed. Furthermore, the committee had considered these issues and a wider range of evidence than the TAVI registry alone, including whether a different analytic approach should have been taken. The panel heard that a different approach to evidence searches and selection may have led to a different outcome, but also noted that the resolution process does not cover disagreements surrounding scientific or clinical interpretation or judgement, including the weight given to one piece of research or evidence over another.

Action required: Whilst the panel did not find that the approach was fundamentally flawed, they concluded that the decisions made regarding evidence searching and selection should be reviewed by the committee (see also below).

Resolution request 2

Submitted in response to the guidance in general and also referenced section 1. Please note that the request covered several different claims, of which many the initial scrutiny panel did not consider to be grounds for resolution. The parts of the request relevant to the panel discussion are reproduced here, with the full text and NICE's response to the part not upheld in Appendix B. The panel is asked to consider whether resolution grounds of breach of process have been met.

Comment text

The Reliance of the TAVI LSA on the original NG208 findings (2021)

NG208 is outdated and flawed in numerous respects. However, this general approach has framed the value assessment and created several factual, perverse, and discriminatory outcomes.

Reliance on the original NG208 findings appears to stem from the original stated goal for LSAs (first draft of Interim Methods and Process) of using a predetermined price range against which technologies would be evaluated – a concept that was introduced in March 2024, long after the TAVI LSA had commenced.

We highlighted this concern about a pre-determined price range in numerous correspondence and during a TEAMS video conference at which Dr Sam Roberts was present, in March 2024, so it is deeply concerning to reach the resolution phase without these points being addressed. The cumulative effect of all the individual concerns is that the entire draft guidance is simply not fit for purpose in its current form, and unfairly prejudices our products despite

their robust data to demonstrate cost-effectiveness and full range of indications, which other products in the LSA lack.

For instance, the LSA is described as being intended to assess "*whether price variations between technologies in a category are justified by differences in innovation, clinical effectiveness and patient benefits*." However, the use of the original cost-effectiveness model from NG208 does not do this and undermines that intention. That model compared TAVI with surgery and was based on only two devices (SAPIEN and Evolut platforms) among the eleven TAVI valves within the LSA scope.

…

By incorporating reference to the NG208 into this LSA draft guidance, which was only seen in the first draft guidelines publication and had not been previously mentioned, the implication is that NICE deems NG208 still up-todate and sound when, irrespective of the flaws we highlighted above, it is now completely outdated and should not be seen to provide any reliable context in the present day.

Moreover, incorporating the already outdated NG208 into new guidance (as NICE is seeking to do here), which itself is unlikely to be reviewed for several years, compounds the issue. This approach also contradicts Principle 13 of NICE's principles, which states that "*NICE's guidance and standards need to be up to date to ensure people receive the best care and advice, and to be credible for health and social care professionals, commissioners and providers*."

Comments from NICE team

The company claims that cross-referencing NICE's guideline on heart valve disease (NG208) in the guidance represents a breach of process. It relates this claim to the draft interim process and methods statement concept of a predetermined price range, which was to be determined externally without using health economic analysis. This concept was not carried through to the

final statement and is not applicable to the thresholds derived in NG208. All reference to NG208 is provided for context only. The economic analysis done by the EAG for this assessment used a model that was based on the model used in NG208, but was adapted to allow cross-product comparisons. The committee concluded that the model results were too uncertain to determine whether there were differences in the cost effectiveness of the transcatheter heart valves (see section 3.20 in the guidance). Therefore, no clear recommendation on the relative cost-effectiveness of different valves could be made.

However, the aim of LSA is to support procurement and commissioning decisions (see the interim LSA methods and processes statement). All TAVI valves are procured through a framework developed with NHS Supply Chain, which is periodically renewed. The interim statement says that the committee recommendations can describe affordability, procurement and commissioning considerations. The committee concluded that it is important that users consider value for money, which they can do by referring to NG208, which assessed the cost-effectiveness of TAVI as a class vs surgery. This is a recent analysis which the committee agreed was still valid and relevant (see section 3.21 in the guidance). NHS Supply Chain have communicated to NICE that they already consider the analysis from NG208 in their negotiations with suppliers, so this recommendation is reinforcing that this is the best available analysis for this purpose.

NICE has a well-established process for stakeholders to notify the need for a guideline update (see Prioritising our guidance topics). The Centre of Guidelines also has a well-established process for developing guidelines that includes stakeholder feedback. Since its publication in 2021, no concerns have been raised on the validity of NG208 and no notifications have been received requesting an update of the guidance. It is beyond the remit of LSA to reanalyse the cost effectiveness of TAVI compared with surgical valve replacement.

There is significant precedent for cross-referencing of NICE outputs within guidance, see for example NICE's diagnostic guidance on Quantitative faecal

immunochemical testing to guide colorectal cancer pathway referral in primary care and NICE's early value assessment of Digital technologies for delivering multidisciplinary weight-management services.

Initial scrutiny decision

Grounds for resolution referred to panel on potential breach of process only.

Response from Edwards Lifesciences

The original NG208 economic model is outdated and flawed in numerous respects. However, the committee's reliance on this model lacked transparency, framed the procurement recommendation, and created several factually inaccurate, perverse, and discriminatory outcomes.

NG208 unfit for purpose

NICE justifies the use of the original NG208 model in this LSA by suggesting that it was used for context only (the meaning of which NICE has failed to make clear). However, the original NG208 model is fundamentally unfit for purpose, as we clearly set out in Resolution Request 2. NG208 compares TAVI with surgery based on only two devices among the eleven TAVI valves within the scope of this LSA, relies on outdated assumptions not reflective of current TAVI practice, and contains errors that were addressed in Appendix 1 of our Resolution Comments document (20 Dec 2024). In addition, NG208 did not include certain post-discharge complications which could affect costeffectiveness.

This LSA should not have used the original NG208 model in any capacity (including "for context"), as it addressed a different decision problem (TAVI vs. surgery). As noted in Resolution Request 2 (please see Appendix B below), since the publication of NG208, there have been many high-quality costeffectiveness publications which this LSA should have incorporated. The EAG should therefore have developed a new model properly addressing the decision problem – specifically, an incremental cost effectiveness analysis based on all available evidence (not just the UK TAVI registry with various

indications and unbalanced samples sizes) and in line with the indications for use for each of the TAVI devices.

Use of NG208 lacked transparency

Moreover, to suggest that original NG208 model was merely used for context drastically understates the influence this guideline had on the committee's conclusions. As noted in our response to NICE's initial scrutiny, the committee placed substantial weight on the original NG208 model in reaching its decision. Accordingly, a fully executable version of that model should have been offered during consultation (a point also confirmed by the Court of Appeal in *R (otao Eisai) v NICE*). In stark contrast, the cost-effectiveness outcome from original NG208 model was opaquely introduced in the closed section of the first committee meeting, leaving stakeholders in the dark as to how the committee considered it. Irrespective of any arguments for the merits of using the original NG208 model in this LSA (which we do not accept), the egregious lack of transparency surrounding its use self-evidently undermines NICE's processes and led to the committee forming its conclusions based on flawed assumptions without the opportunity for proper stakeholder input.

Illogical conclusions drawn from NG208

In any event, the fact that NICE deems the LSA model results too uncertain to state whether there are differences in cost effectiveness between the devices, means that it cannot be extrapolated to support the argument that there is no evidence to justify differences in price. First, to state that there is insufficient evidence betrays a distinct lack of thoroughness, given that Edwards submitted substantial relevant evidence to NICE and the EAG itself refers to an abundance of evidence that it could not assess due to time constraints. Second, uncertainty in the model results does not prove that there is no evidence to justify price differences. The only logical outcome from this uncertainty would be for NICE to recommend that the supply of TAVI devices to the NHS continues as it does currently, while further evidence is identified and evaluated. By contrast, in this LSA, the committee irrationally determined that given the uncertainty of the adapted model on justifying price differences, the

original NG208 model is preferred and provided for “context” only. This clearly demonstrates that the opaque and *ad hoc* process followed in this LSA, including the unfair reliance on the original NG208 model, resulted in the committee drawing flawed conclusions.

Use of NG208 undermined NICE’s usual standards

NICE cites precedent for the cross-referencing of NICE outputs within guidance. However, as we have explained, the use of the original NG208 model in this manner is not appropriate in this LSA. Not only is the original NG208 model severely outdated, but it is also not relevant to the decision problem.

If NICE had conducted this assessment as a multiple technology appraisal (MTA) under the medicines evaluation programme, it would not have taken this approach and certainly would not have relied on the assumptions used in the original NG208 model. Applying a less rigorous standard to TAVI devices seems illogical and is deeply concerning. With respect to the TAVI devices, there are numerous technologies and abundant evidence, enabling comparisons between devices and with surgery (if that element was also required), and NICE is making recommendations that comment on clinical and cost efficacy and ultimately impact price. The reasonable approach here would therefore be to develop a tailored model and base the assessment on a thorough, transparent and well-structured process – all of which this LSA notably lacked.

Other comments

NICE also provides in its response that NHS Supply Chain has communicated to NICE that it considers the analysis from NG208 in negotiations with suppliers. This statement is irrelevant in the context of this LSA – NICE has relied on outputs from a guideline that does not address the decision problem (namely, TAVI vs. TAVI comparison, not TAVI vs. surgery comparison); whether NHS Supply Chain uses the guideline in negotiations is not material to determining whether NICE has breached its processes in this respect.

NICE also states that it has "*a well-established process for stakeholders to notify the need for a guideline update*," and that "*no concerns have been raised on the validity of NG208*." This is simply not true. Edwards provided feedback on the draft scope in late 2023, which flagged the following:

"*The economic analysis developed for NICE guideline 208 included, as previously highlighted, methodological issues and flaws in the model such as:*

- *Assumptions considered in the model were outdated and not reflective of current TAVI practice, such as the consideration of a significant relative survival reduction after TAVI vs. general population or the short-term adverse events incidences.*
- *Various relative treatment effects of TAVI (vs. SAVR) were based on a combination of 3 RCTs: PARTNER 2, PARTNER 3 and Evolut LR. The combined effects (calculated hazard ratios) mixed valve generations (2nd and 3rd), type of TAVI valves (balloon vs. self-expandable), indications (intermediate and low-risk patients), and TAVI approaches (transfemoral and transapical).*
- *The results from this guidance do not reflect the QALY gains seen in other HTAs and/or publications."*

As is clear, and as we highlighted to NICE on several occasions, the original NG208 economic model is outdated, flawed and unfit for use in this LSA. The committee's reliance on the original NG208 model in reaching its recommendations therefore represents a serious breach of process and falls far short of the rigour, transparency and thoroughness expected of the Institute.

We therefore request that, at a minimum, all references to NG208, including both the statement from recommendation 1.3 "Value for money should be determined considering the effective price for transcatheter heart valves described in NICE's guideline on heart valve disease" and the sections in "What this means in Practice" that rely on the original NG208 model be removed from

the guidance in this LSA. Specifically, the following bullet points, or their proposed updates, per RR1:

"'Added value' agreements between companies and NHS Supply Chain allow for part of the cost of a valve to be returned to the NHS or to an NHS trust based on the number of valves purchased. At their list prices (before accounting for these agreements), many transcatheter heart valves cost more than the cost-effective prices identified in NICE's guideline on heart valve disease presenting in adults: investigation and management (NG208). Even after accounting for 'added value' agreements, the NHS may benefit more from negotiating lower list prices. This is because 'added value' agreements may not release resources for the NHS." And "The economic evaluation done for NG208 comparing TAVI against surgical valve replacement showed that TAVI is cost effective for people who are at high surgical risk or for whom surgery is inappropriate if the transcatheter heart valve costs £18,000 or less. But, the valve would have to cost £14,800 or less for TAVI to be cost effective across all surgical risks."

Panel response to resolution request 2

Ground 1: met

Summary: The panel heard from the stakeholder that the committee had relied excessively on the findings of NG208, arguing that while it was appropriate to adapt the model from NG208 to this LSA's decision problem the original NG208 model was not suitable for cross-referencing cost-effectiveness thresholds due to changes in the available TAVI devices and clinical practice during recent years. The applicability of NG208 as context when considering value for money was also questioned since it compares TAVI to surgery and the cost effectiveness analysis that underpins NG208 has not been updated in light of more recent evidence. The panel noted that as a result of the resolution process a change has already been made to the LSA guidance to address a factual inaccuracy in the text.

Action required: The panel concluded that NICE should reconvene the guidance committee to reconsider the relevance of NG208 to cross-reference cost-effectiveness thresholds and the determination of value for money in this LSA.

As noted above, the panel also concluded that the reconvened committee should review the approach to searching for and selecting evidence in this LSA.

Resolution request 3

An additional breach of process point was raised by Edwards Lifesciences following the initial scrutiny process, highlighting that an addendum to the external assessment report produced for the second committee meeting had not been shared with the company alongside the final draft guidance at the beginning of the resolution period. The full letter received is reproduced in appendix C.

Comment text

NICE also failed to provide visibility or opportunity to comment on the extensive External Assessment Report Addendum detailing the reasons for the determination of “not key evidence” of certain clinical data. The reasoning given in this document, which was sent to us on request on 30 January 2025, represents a clear case of double standards with regard to “scientific opinion” on which evidence is relevant, given that the justification for rejecting evidence in many cases also applies to NG208 (on which the committee heavily, and unfairly, relied). The failure to distribute such material evidence is also a clear breach of NICE’s Health Technology Evaluations Manual (specifically, Sections 5.8.67 and 5.8.69) and this should be included for discussion in the resolution panel meeting. The breach did not come to light until long after the deadline for the submission of resolution requests in December 2024.

Comments from NICE team

The external assessment group (EAG) was asked to produce an addendum to their report following consultation on the draft guidance, to review the substantial amount of evidence submitted by stakeholders and assess its applicability and relevance to the decision problem for consideration by the committee.

The company is correct that section 5.8.67 of NICE's Health technology evaluations manual states:

"When NICE sends the final draft guidance to stakeholders, any further analysis done by the company, NICE or the EAG during development of the final draft guidance will be made available to stakeholders. Comments received on the draft guidance (if produced), together with NICE's responses to them are also provided."

The company was provided with the final draft guidance and consultation comments and responses on 29th November 2024 when the resolution period began, but the assessment report addendum was not included. This was an error, and upon notification from the company the addendum was shared as soon as possible.

However, the company had received the slides for the second committee meeting on the 16th October 2024, which included a detailed summary of the addendum for committee discussion. The addendum was also referred to in the responses to consultation comments. Therefore, the company was aware an addendum had been produced, and of the content and conclusions of the additional work, from the time of the second committee meeting. The NICE team apologises for not sharing the full addendum at the appropriate time, but does not consider this error to have significant impact on the conclusions of the committee (as the full addendum was provided to committee a week before the second meeting) or the wording of the final guidance.

Response from Edwards Lifesciences

NICE's comments accept that the Institute's failure to share the External Assessment Report addendum with stakeholders breaches the HTA manual. NICE attempts to justify this breach on the basis that Edwards received a "*detailed summary of the addendum for the committee discussion*." The extent of the "detailed summary" to which NICE refers was as follows:

- Slide 5: "*Additional work undertaken by the EAG is reported in an addendum to the EAR, shared with stakeholders as part of the committee papers pack*."

- Slide 10: "*In response to comments received during consultation on the draft guidance, the EAG reviewed and summarised 44 additional pieces of evidence in a supplementary report, published as an addendum to the EAR. The EAG compared the results of studies considered key evidence with the results of the UK TAVI registry analyses and published evidence already considered within the original EAR, to determine general trends*."

- Slide 11: "*In its report, and in the addendum, the EAG set out the strengths and limitations of using real world data versus using data from multiple published studies to populate the economic model*."

Contrary to the statement in Slide 5, the addendum was not shared with stakeholders as part of the committee papers pack. As is clear from the above, the slides did not provide any detail as to why the EAG rejected studies, or that the EAG considered many of them to be in scope but not "key evidence."

We received the consultation themed comments and responses document on 29 November 2024, which provided some further limited detail as to the contents of the addendum, but again failed to clearly identify all the studies which the EAG reviewed (and therefore, it remained unclear which studies remained overlooked) and the reasons why the EAG considered these in scope but not key evidence. The fact remains that NICE should have circulated the full addendum and allowed comments on it ahead of the final committee meeting which took place six weeks earlier on 17 October 2024. Given that the

addendum had been finalised on 9 October 2024, NICE should have provided the addendum to stakeholders, allowed appropriate time for review and comment, and postponed the second committee meeting.

Resolution of this matter would involve halting the LSA process and returning to the point where all stakeholders are provided with the addendum and given the opportunity to comment. Those comments should then be reviewed and presented to the committee. Alternatively, as the contents of the addendum are now known, all evidence that had been submitted and overlooked plus all of the references that were considered “not key evidence” and rejected due to reasons prevalent in the original NG208 model should be included and a new analysis undertaken.

Panel response to resolution request 3

Ground 1: not met

Summary: The panel heard evidence that an addendum to the external assessment report produced for the second committee meeting had not been shared with the company alongside the final draft guidance at the beginning of the resolution period. NICE agreed that an error had been made, and this was corrected subsequently. Having heard further evidence, the panel concluded that this error had not fundamentally compromised the integrity of the final guidance.

Action required: None required.

Appendices

Appendix A: Resolution request 1

Full text of submitted comment.

Comment text

Fundamentally flawed approach

The process followed in this appraisal fell far short of the standards required of NICE. NICE publishes procedures to ensure appraisals are carried out with necessary rigour and thoroughness, which safeguards the validity of the recommendations NICE makes at the conclusion of an appraisal. In this instance, the whole of the appraisal process lacked direction or a clear framework to guide it, as exemplified by the fact that the appraisal began without any formal methods or process in place.

Even when NICE published an interim methods and process guide for Late Stage Assessments ("LSAs") four months into the TAVI assessment, there remained many instances of a lack of clarity and deviation from NICE's normal methods. Certain key procedural decisions that NICE took departed materially from the established process and contributed to an incomplete and partially sighted review of the evidence. For example, the draft scope was published immediately ahead of the scoping meeting and there was no formal consultation period, with stakeholders only granted 24 hours to submit comments. Further, there were various examples of deviation from the intended methods throughout the running of the appraisal. As a result, the process itself lacked transparency, and has led to draft guidance which does not respect the licensed indications for the products, nor does it seem to allow NICE to make a particular reference to technologies within the group which have clear evidence to support their cost-effectiveness. Leaving aside that this LSA materially departed from the interim procedure, the LSA process itself was unfit for purpose, and NICE should have instead considered

conducting the appraisal through single technology appraisals for each product.

The various procedural deficiencies also resulted in several factual errors, which we set out in detail in this comments document. For reference, we list the key timings in this appraisal below:

Topic selected and “in progress”	17.10.23
Registered as stakeholder	18.10.23
Request for product and clinical information (no prior notification)	10.11.23 (deadline 24.11.23)
Invitation to scoping workshop received (no prior notification of date)	21.11.23 (date of meeting 30.11.23)
Product and clinical information returned	24.11.23
Online meeting with LSA team	29.11.23
Draft scope received	29.11.23
Scoping meeting (informed that there would be no consultation, but we could send a response letter if received by close of business on Dec 1st)	30.11.23
Comments letter (on draft scope) sent	01.12.23
Final scope published	08.12.23
Edwards letter commenting on final scope	Part one: 20.12.23; Part two: 15.01.24

There are several notable examples of the pervasive lack of consistency, transparency and adherence to established process in this appraisal:

- The use of the UK TAVI registry here represents a concerning lack of consistency between LSAs. NICE’s draft guidance states at Section 3.6: “*The EAG explained that it considered the UK TAVI registry (see section 3.8) the strongest source of clinical evidence. This is*

because it provided recent data from the UK and allowed the assessment of different valves." The reliance and preference for NICOR data has led to many factual errors and the conclusion that "*the results from an economic evaluation based on real-world data analyses in the UK are* ***too uncertain***" (emphasis added).
The use of NICOR evidence is inconsistent between LSA assessments. In complete contrast to the assessment here, the LSA for drug eluting stents (GID-HTE10039) gives the following reasons for **NOT** using the registry:

- Presence of confounding in registry data factors, e.g., disease severity or lesion complexity are not consistently recorded, making it difficult to attribute outcomes captured directly to stent choice.
- A limited number of the technologies in scope being recorded in NICOR database.
- Length of follow-up limited by the time the technology has been available in the NHS.
- Long-term/mortality outcomes sourced from HES/ONS cannot reasonably be attributed to stent choice.

The first point listed above "confounding in registry data factors" as a reason to NOT use NICOR data is also exemplified in the following statement at Section 3.8 on page 13 of the draft guidance, which also demonstrates process failings: "*Clinical experts stated that the UK TAVI registry was not designed to make direct valve comparisons and several clinically important patient characteristics (see section 3.3) are not recorded in it. The EAG also highlighted that many fields in the registry were poorly completed*."

- Given that the TAVI registry was not fit for purpose for the decision problem (making comparisons between valves, which is needed to draw conclusions on price variation), other evidence should have been reviewed. This would have ensured the committee was presented with all of the appropriate

evidence and would be in a position to determine which evidence was the most relevant. In deciding what evidence was most relevant, the non-systematic review process choices made by the EAG failed the committee and breached NICE's process.

The final point listed above “Long-term outcomes cannot reasonably be attributed” is exemplified in the TAVI LSA, as the EAR states (p173): “*A limitation of the approach is that these events are not necessarily associated with having a TAVI*.”

We would agree with the approach taken for drug-eluting stents, which NICE should apply consistently (including in this appraisal) or otherwise provide adequate justification for departing from it. Failure to do so represents a breach of process.

- At Section 3.12, The statement “Five transcatheter heart valves (Allegra, Evolut FX, Hydra, Myval Octacor and Trilogy) had no data in the UK TAVI registry because they were new to the NHS Supply Chain framework at the time of assessment” highlights a breach of process. If the TAVI registry data was used as the basis for decision making and if there is not data in the TAVI registry for these valves, then the guidance section should state that no data was available to evaluate these valves and they should be excluded from the guidance. Including them despite there being no evidence in the preferred registry data “does not add up,”[1] and has led to inaccurate conclusions.

Various statements in the guidance are not consistent with NICE following the LSA process. Key evidence consistent with the scope and decision problem for this LSA has been ignored, and the EAG chose not to systematically review evidence that was relevant. It is not sufficient to ignore relevant evidence by putting forward an argument that the TAVI registry was the most relevant, before systematically reviewing all evidence relevant to the decision problem. This approach is illogical.

An appropriate resolution here is to start again, to ensure that the process itself allows individual technologies to be recommended where the evidence allows, if needs be through individual single technology assessment processes.

[1] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2735762

NICE response to resolution request 1

Following review, the NICE team considers part of this resolution request relating to the lack of process at topic launch and departing from the interim methods and process statement to contain potential grounds for resolution on breach of process. This issue will be discussed at the panel meeting.

The team does not believe that the remainder of the request constitutes grounds for resolution on factual errors or breach of process, and the response to these points is presented here:

Section 7.2.5 of NICE's health technology evaluation manual explains that grounds for resolution on factual inaccuracies only apply where "*a factual error is an objective error of material fact in the final draft guidance*" and that "*conflicting scientific or clinical interpretations or judgements are not considered to be factual errors*".

The company has highlighted that there was no consultation on the draft scope as a deviation from process. During the preparation of the interim methods and process statement for late-stage assessment, the process for this assessment was based on diagnostics assessments, as the process best suited to multiple technology evaluations. Section 2.5.6 of NICE's HTA manual states that "*For diagnostics evaluations, NICE normally holds a scoping workshop and does not have a consultation on the draft scope*." Although no consultation took place, stakeholders were given the opportunity to comment on the draft scope by email to ensure all relevant points had been considered.

The company claims that the external assessment group (EAG's) decision not to conduct a systematic review represents a ground for resolution on breach of process. Following scoping, NICE included a number of additional steps to the process in order to ensure that the assessment was as robust as possible and that no relevant evidence was missed. These included:

- Pausing the assessment so that a formal public consultation on the interim process and methods statement could be done.

- Asking stakeholders to submit evidence during the assessment stage (request for information to companies).
- Giving stakeholders the opportunity to submit additional evidence during the assessment stage (factual accuracy check of the assessment report).
- Giving stakeholders the opportunity to submit additional evidence during the guidance consultation stage (public consultation on the draft guidance).
- Extending timelines to allow the EAG to review the submitted evidence and produce an addendum to the assessment report.

Section 4.8 of NICE's interim methods and process statement for late-stage assessment states that "*The evidence reviews may be done using pragmatic approaches when appropriate*." This was appropriate for this LSA, in which a systematic review would have identified an infeasibly large amount of evidence with a marginal benefit of conducting it.

The company claims that "*Key evidence consistent with the scope and decision problem for this LSA has been ignored*". This has the potential to lead to factual inaccuracies if such evidence exists. It is not clear which relevant evidence the company believes has not been considered. All evidence submitted by the companies was reviewed by the EAG and presented to the committee for consideration.

The company claims that the "*Draft guidance […] does not respect the licensed indications for the products*". The guidance states "*Use a transcatheter heart valve that is clinically appropriate*". All NICE HealthTech guidance implicitly includes the provision that the product should be used within its intended use in line with UKCA or CE marking, and only if it is explicitly to be used off-label would this be stated. This has been confirmed by the NICE content team.

The company has queried the committee's preference for data from the UK TAVI registry in contrast to the stents LSA (GID-HTE10039). The committee's choice to consider the UK TAVI registry the best available data source represents its own conclusion, and the circumstances differ from the LSA on coronary stents. There is no requirement for the committee's preferred evidence source to be the same across LSAs. This is because each technology has its own specific considerations relating to the clinical context and evidence base. Within the current LSA, the EAG explained its rationale for prioritising real-world data in the protocol and in the assessment report, as well as in the committee meetings. Other evidence was considered by the EAG during the assessment and following consultation to ensure that relevant evidence had not been missed. The company's claims that using these data leads to factual inaccuracies relies on the assumption that there are better and more suitable data and that the committee's conclusions would have been different if such data were available and considered. We do not believe this to be the case and are confident that the committee received and considered the best available evidence.

The company claims that the lack of data in the UK TAVI registry for 5 valves represents a breach of process. It claims the "*TAVI registry data was used as the basis for decision making*", which is not correct. The guidance states that "*The EAG explained that it considered the UK TAVI registry (see section 3.8) the strongest source of clinical evidence*." The committee used the combined clinical (including published evidence) and economic evidence, as well as expert advice for its decision making. Published evidence was considered on these valves.

Appendix B: Resolution request 2

Full text of submitted comment.

Comment text

The Reliance of the TAVI LSA on the original NG208 findings (2021)

NG208 is outdated and flawed in numerous respects. However, this general approach has framed the value assessment and created several factual, perverse, and discriminatory outcomes.

Reliance on the original NG208 findings appears to stem from the original stated goal for LSAs (first draft of Interim Methods and Process) of using a predetermined price range against which technologies would be evaluated – a concept that was introduced in March 2024, long after the TAVI LSA had commenced.

We highlighted this concern about a pre-determined price range in numerous correspondence and during a TEAMS video conference at which Dr Sam Roberts was present, in March 2024, so it is deeply concerning to reach the resolution phase without these points being addressed. The cumulative effect of all the individual concerns is that the entire draft guidance is simply not fit for purpose in its current form, and unfairly prejudices our products despite their robust data to demonstrate cost-effectiveness and full range of indications, which other products in the LSA lack.

For instance, the LSA is described as being intended to assess *"whether price variations between technologies in a category are justified by differences in innovation, clinical effectiveness and patient benefits*." However, the use of the original cost-effectiveness model from NG208 does not do this and undermines that intention. That model compared TAVI with surgery and was based on only two devices (SAPIEN and Evolut platforms) among the eleven TAVI valves within the LSA scope. It also has several limitations that we have previously shared with NICE (please see comments on the first draft guidance) and summarize below:

We have identified various methodological issues and flaws, and some assumptions are outdated and not reflective of current TAVI practice (relative survival reduction after TAVI vs. general population or short-term AEs rates). Please see Appendix [B2] for a detailed discussion of the flaws in NG208, along with eleven other limitations shown on page 147 of the EAG report.

Various relative treatment effects of TAVI (vs. SAVR) based on a combination of three RCTs: PARTNER 2, PARTNER 3 and Evolut LR trials. Treatment effects seem to be calculated from studies mixing indication (IR vs. LR), valve generation (SAPIEN XT vs. SAPIEN 3), interventional approach (TA vs. TF) and type of valve (BE vs. SE).

Moreover, NG208 did not include certain post-discharge complications which could affect cost-effectiveness. It therefore cannot be relevant to the decision problem and while presented to the committee for context, should not be used as the basis for a recommendation.

Since the publication of NG208, there have been many high-quality cost-effectiveness publications which show comparisons of the valves involved in the LSA (see full list on page 11). One of these is a UK based study of Evolut four-year data, with TAVI improving survival by 0.41 life years and added 0.28 QALYs at incremental cost of £5,021, resulting in a lifetime ICER of £17,883 per QALY gained2;

[redacted]

By incorporating reference to the NG208 into this LSA draft guidance, which was only seen in the first draft guidelines publication and had not been previously mentioned, the implication is that NICE deems NG208 still up-to date and sound when, irrespective of the flaws we highlighted above, it is now

completely outdated and should not be seen to provide any reliable context in the present day.

Moreover, incorporating the already outdated NG208 into new guidance (as NICE is seeking to do here), which itself is unlikely to be reviewed for several years, compounds the issue. This approach also contradicts Principle 13 of NICE's principles, which states that "*NICE's guidance and standards need to be up to date to ensure people receive the best care and advice, and to be credible for health and social care professionals, commissioners and providers*."

In addition, NICE's flawed reliance on NG208 led to several factual errors in the draft guidance. For instance:

At Section 1.3, the draft guidance states: "*Value for money should be determined considering the cost-effective price for transcatheter heart valves described in NICE's guideline on heart valve disease*." This statement is incorrect and should be removed or, alternatively, replaced with "*clinically appropriate technologies should be able to demonstrate cost-effectiveness according to their indications and pricing through robust peer-reviewed evidence*."

The following statement provided at '*What this means in practice*' on page 3 of the draft guidance is also incorrect as a result of the reliance on NG208: "*The economic evaluation done for NG208 comparing TAVI against surgical valve replacement showed that TAVI is cost effective for people who are at high surgical risk or for whom surgery is inappropriate if the transcatheter heart valve costs £18,000 or less. But, the valve would have to cost £14,800 or less for TAVI to be cost effective across all surgical risks*." According to the EAG report, "*Clinical Experts have indicated that the majority of TAVI procedures in the UK NHS continue to be performed in those considered high risk for surgery*." As such, to state that the price would need to be £14,800 or less to be cost effective in the UK TAVI population is a factual error, as it relies on a

much higher use in place of lower risk surgery than is the reality in the UK. At Sections 3.2 and 3.4, the draft guidance notes that "*TAVI is primarily used in people who are at high risk for open heart surgery or for whom surgery is inappropriate*."

In a response to comments on the first draft guidance, NICE stated "*The aim of this assessment was to determine whether price differences between transcatheter heart valves could be justified, and not to determine a costeffective price for a transcatheter heart valve compared with surgical valve replacement, which was evaluated in NG208*." Also, in the slide presentation to the second committee meeting, 17th October 2024, the EAG states very clearly that "*The purpose of this late-stage assessment is not to determine the cost-effectiveness of TAVI compared with surgery*." However, the use of NG208 in the recommendations has completely contradicted both of these statements.

Any reference to the NICE guideline (NG208) is out of process and should be removed. The EAG's revised model should form the basis of the recommendations, not NG208. If the committee used the original NG208 model as the basis for its decisions, then a fully executable version of that model should have been offered during consultation, as indicated in Section 4.5/4.21 of the interim guide. This is also in line with the principle of transparency (see the Court of Appeal case in R (otao Eisai) v NICE).

In the absence of any methods and process, we also relied on the following assurances from Mark Chapman (Director for HealthTech-CHTE at NICE) in an email dated 1 February 2024: "*please be reassured we will not generalise evidence for licenced indications to those products that are not licenced for use in a given population. This should have been made clearer in our response to yourselves and ABHI. It is important evidence is rewarded and NICE does recognise this in our programmes where we often recommend those with evidence versus those without*." We therefore had a legitimate

expectation that NICE would conduct the LSA on this basis, which NICE subsequently undermined.

An acceptable and critical resolution is for all references to the costeffectiveness data from NG208 to be removed from the guidance and for the process to be conducted without reliance on this outdated guidance, including as a basis for pricing.

Appendix [B2] – Flaws in NG208

Short-term estimates within the 1st cycle of the model (30 days)

- Estimate for Moderate / Severe PVL for TAVI at 30 days is wrong as it is coming from an estimate at 1-year follow-up. Indeed, the 2.7% estimate for Moderate/Severe PVL used in the NICE model for TAVI corresponds to a 1-year estimate (not at 30 days) from the SOURCE 3 registry, which was published in 2017 publication by Wendler at al.3 Moreover, this 1-year estimate was not based on a low-risk population but on a high-risk cohort with a logistic EuroScore of 14% for the TF cohort. This is important as this reflects an increased risk ratio for TAVR > 10, as the estimate considered for SAVR is 0.2%. Using the 30-days data from the PARTNER 3 trial (0.8% for SAPIEN 3 and 0% for SAVR), the impact on the results would be significant as the model is highly sensitive. The incremental QALY gain would increase to 0.04 (+69%).
- Stroke incidence for both groups TAVI and SAVR at 30 days. The 2.1% estimate for TAVI in the NICE model is coming from the 2019-2020 NICOR dataset.[4] A risk ratio of 0.83 was used (TAVI vs. SAVR), based on a review of many RCTs (including trials conducted for intermediate risk patients, 2nd generation of TAVI valves, and alternative non-transfemoral access), leading to a 2.5% stroke incidence estimate for SAVR. If we consider data from our latest PARTNER 3 trial for low-risk patients, the corresponding incidence rates are slightly different with a larger difference between SAPIEN 3 and SAVR (0.6% vs. 2.5%, RR = 0.25). Using these two estimates completely changes the results of the model. The incremental QALY gains double and increases to 0.051 (+116%).
- Major bleeding incidence for both groups TAVI and SAVR at 30 days. The 2.3% estimate for TAVI in the NICE model is coming from the 2019-2020 NICOR dataset. A risk ratio reduction of 0.24 has been estimated based on a review of many RCTs (including trials conducted for intermediate risk patients, 2nd generation of TAVI valves, and alternative non-transfemoral access), leading to an estimate for SAVR of 9.4%. If we consider data from our latest PARTNER 3 trial for low-risk patients, the corresponding incidence rates are slightly different with a larger difference between SAPIEN 3 and SAVR (1.2% vs. 11.9%, RR = 0.1). Using these 2 estimates slightly changes the results of the model, as the incremental QALY would increase to 0.03 (+27%).
- Permanent pacemaker incidence for both groups TAVI and SAVR at 30-days. The 9.7% estimate for TAVI in the NICE model is coming from the 2019-2020 NICOR dataset considering both balloon-expandable and self-expandable valves. An increased risk ratio of 1.81 (vs. SAVR) has been estimated based on a review of many RCTs (including trials conducted for both balloon-expandable and self-expandable valves), leading to an estimate for SAVR of 5.4%. The large difference in permanent pacemaker between the 2 types of valves is well-known and is also reflected in the 2019-2020 NICOR dataset (slides #60-61), with a 7% incidence for the balloon-expandable SAPIEN 3 valve vs. 14.8% for the self-expandable valve. The 7% incidence with SAPIEN 3 is actually very close from the TAVI with SAPIEN 3 arm of the PARTNER 3 trial (6.6%). The difference between SAPIEN 3 and SAVR became much smaller with 6.6% and 4.1% for SAPIEN 3 and SAVR respectively (RR = 1.65). Plugging the PARTNER 3 results with these two estimates slightly changes the results of the model; the incremental QALY increases to 0.03 (+27%)

- Mortality estimates at 30 days for both groups TAVI and SAVR. The 30-days mortality considered for SAVR is 0.7% and is coming from the National Adult Cardiac Surgery Audit (NACSA) report,[5] but we were not able to find this figure in the report referred in the economic report of the NICE guideline (NG208). A reduced risk (RR = 0.81) is applied for the 30-days mortality for TAVI – estimated from a review of many RCTs (including trials conducted for intermediate risk patients, 2nd generation of TAVI valves, and alternative non-transfemoral access) leading to a 30-days mortality of 0.6% for TAVI. If the 0.6% 30-days mortality for TAVI is not too far from the one in PARTNER 3 (0.4%), we are surprised about the 0.7% for SAVR – which strongly outperforms the 1.1% from the surgical arm in PARTNER 3 and its legitimacy could be questioned. When looking into more details from the NACSA report, we find crude mortality rate for all cardiac procedures with a 2.44% estimate but no stratification for isolated SAVR and by risk scores. A quick review of "contemporary" real-world evidence comparing 30-days mortality between TAVI and SAVR for low-risk patients have been produced (see Appendix B3). The mortality at 30 days in the NICE model appears low compared with the literature (ranges from 1.1% to 3.6%), so the 0.7% from NICE does appear to be underestimated. If we consider data from our latest PARTNER 3 trial for low-risk patients, the difference in 30-days mortality between SAPIEN 3 and SAVR (0.4% vs. 1.1%, RR = 0.37) increases. Using these 2 estimates changes slightly the results, and the incremental QALY increases to 0.027 (+14%).

    - When combining these changes all together to the 30-day events described above, **the impact is substantial:**

30-days Events	NICE (TAVI/SAVR)	PARTNER 3 (TAVI/SAVR)	Δ Cost	Δ QALY	ICER
NICE Base Case			**+ £ 3 300**	**+ 0.024**	**£ 139.8k**
Conv. SAVR	0.55% / NA	0.2%	+ £ 3 287	+ 0.029	£ 113.1k
Mod/Sev PVL	2.7% / 0.2%	0.8% / 0.0%	+ £ 3 300	**+ 0.04**	**£ 77.3k**
Stroke	2.1% / 2.5%	0.6% / 2.4%	**+ £ 2 401**	**+ 0.051**	**£ 47.1k**
Bleeding	2.3% / 9.4%	1.2% / 11.9%	+ £ 3 301	+ 0.03	£ 127.5k
Pacemaker	9.7% / 5.4%	6.6% / 4.1%	+ £ 3 321	+ 0.03	£ 122.4k
Mortality	0.6% / 0.7%	0.4% / 1.1%	+ £ 3 160	+ 0.027	£ 117.3k
Combined Effect			**+ £ 2 329**	**+ 0.08**	**£ 27.7k**

The combined effect considering the data from PARTNER 3 at 30 days decreases the incremental cost by 29%, but most importantly **increases significantly the incremental QALY by almost 4-fold up to 0.08**, very close to the 0.1 estimate from the Canadian HTA and the Tam et al. manuscript.

Clinical input for the Markov model in subsequent cycles (from 2nd Month onwards)

- It seems there are inconsistencies in the formulae used between the low-risk and the high-risk model in the extrapolation of monthly utilities between data points during the first year – and we believe the approach and linear formulas used for the high-risk model are accurate (see sheet 'D5 utility' in the NICE model). For example, the utility extrapolation for the 2nd Month (UtilityM2) should be calculated and linearly extrapolated using the following formula:

    - $(Utility_{M6} – Utility_{M1})/5 + Utility_{M1}$ instead of $(Utility_{M6} – Utility_{M1})/4 + Utility_{M1}$

  This issue in the formula occurs also for the subsequent utilities until the 5th Month. The same issues occurred for the extrapolation between the 7th month and the 11th month. For example, the utility extrapolation for the 7th Month (UtilityM7) should be calculated and linearly extrapolated using the following formula:

- ($Utility_{Y1(M12)}$ – $Utility_{M6}$)/6 + UtilityM6 instead of ($Utility_{Y1(M12)}$ – $Utility_{M6}$)/4 + $Utility_{M6}$

This is likely to be a typo or mistake in the formula, which has an impact as it reduces the 1-year utility gains for TAVI from 0.0135 to 0.0162 when corrected (a 20% increase). The model is highly sensitive, as a tiny correction in the utility extrapolation formula in the low-risk model (using the same formula used for the high-risk population) impacts the incremental QALY to 0.026 (+10%).

- Long-term mortality assumptions. This critical component is one of the most impactful in the results of the NICE model. The rationale behind its construction is quite complex and somehow unexpected – knowing the large amount of contemporary evidence existing in the literature nowadays. The long-term mortality calculation for the "Stable" health state is constructed combining 3 assumptions:
    - A significant reduction of the TAVI relative survival versus the general population – specific to intermediate risk (IR) as a reference – based on a study from the UK including 6,420 patients treated with TAVI from 2007 to 2014. The relative survival reduction with TAVI for IR in comparison to the general population are 91.7%, 89% and 85.5% at 1-year, 2-years, and 3-years respectively.
    - A specific hazard ratio of increased morality for HR (2.7) and IR (1.6) vs. LR – based on a study from Israel which includes 1,327 patients treated with TAVI from 2008 to 2014. So, in order to convert IR to LR, a calculated hazard ratio (1/1.6) is applied.
    - A third hazard ratio reducing the TAVI mortality (vs. SAVR) calculated from a clinical review from combined RCTs, including trials conducted for intermediate risk patients with 2nd generation of valve, including alternative access and combining both balloon and self-expandable TAVI valves. The corresponding HR are 0.93 and 0.97 at 1-year and 2-years respectively.

  Then, for the other health states, specific increased hazard ratios are added on top to account for the excess risk of mortality – which is common practice in health economics modelling. However, due to the use of the previous data a 'calibration factor' was used so the mortality in year 3 in the model matches the mortality outcomes of the studies described above.

  Construction of the long-term survival estimates from a combination of 3 various components – including some complex calibration which is difficult to fully understand. One example is that it seems impossible to set exactly equal mortality for TAVI and SAVR – as the whole simulated cohort is being multiplied by the 30-days mortality rate with TAVI (0.7%) and the converted patients to SAVR (0.55%) are also multiplied by this death rate – suggesting that the deaths and other events for these converted to SAVR patients are being double counted. Also, despite a favorable hazard ratio reducing TAVI mortality, the total life-year gains favor SAVR (10.61 for TAVI vs. 10.67 for SAVR), which is counter-intuitive based on the evidence used and is not confirmed by any longer-term evidence.

  The data used from both studies are outdated and do not represent what is expected in clinical practice today in the low-risk population. Patients treated in 2007-2014 did not benefit from our latest TAVI technologies (SAPIEN 3 was introduced in late 2014) and the non-transfemoral approaches represented proportionally a significant number of cases (24% from the 2012 BCIS audit vs. ~5% in the latest one from 2019/2020) – as the catheter diameters were larger. Below a summary table is presented with the various mortality rates considered from NICE, the general population and from our PARTNER 3 trial at 1 and 2-years for the low-risk patients – for both TAVI and SAVR respectively.

Mortality Rates	From NICE	From Gen. Pop.	From PARTNER 3
@ 1-year	7.3% / 7.9%	3.5%	1.0% / 2.5%
@ 2-year	10.7% / 11.0%	6.2%	2.5% / 3.2%

As we can see from the table above, the PARTNER 3 data is outperforming the mortality rate from the general population; thus, life tables from the general population may be more realistic and should be considered, but without any additional excess risk of mortality after TAVI (as seen in economic models described in the literature summarized in the table below).

The all-cause mortality treatment effects considered by NICE are based on combining various RCTs (including trials for intermediate risk patients, 2nd generation of TAVI valves, balloon and self-expandable TAVI valves, and alternative non-transfemoral access) and do not reflect the hazard ratio from the PARTNER 3 trial or the ones calculated from specific low-risk meta-analyses.

Hazard Ratio (HR) – All cause mortality	**From NICE**	**From PARTNER 3**
@ 1-year	0.93	0.41
@ 2-year	0.97	0.75

- When considering the all-cause mortality with TAVI in line with the general population for the low-risk population (changing relative survival with TAVI for intermediate risk to 100% for years 1 to 3 and changing HR for intermediate vs low risk to 1), together with a TAVI treatment effect from the PARTNER 3 trial as reported above, the results change completely. The incremental cost increases slightly by 12%, mostly due to the longer life expectancy, but the incremental QALY gains goes up to 0.187 (almost 8-fold increase), close to the 0.2 estimate from the Zhou et al. publication. The corresponding ICER decreases remarkably to £19,738/QALY, which represents an 86% reduction versus the NICE base case.

- Aortic valve re-intervention. The assumption of an increased risk for TAVI, with a calculated HR = 1.87, is based on a compilation of many RCTs, including trials with intermediate risk patients (2nd generation of TAVI valves removed from the UK market in 2014), balloon and self-expandable TAVI valves, and alternative non-transfemoral access. The latest 5-year available data with SAPIEN 3 from the PARTNER 2 S3i cohort, assessing and comparing the 5-year incidence of structural valve deterioration (SVD) using the latest VARC 3 criteria between SAPIEN XT, SAPIEN 3TM and SAVR was not considered. In this trial, the various rates of SVD (SVD-related bioprosthesis valve failure (BVF), and all-cause BVF) with SAPIEN 3 were not different to SAVR and were significantly lower versus SAPIEN XT. This was also confirmed in the recent 5-year follow-up of the PARTNER 3 trial (specifically for low-risk patients). Considering the latest data with SAPIEN 3 and a corresponding HR = 1 (no difference), the impact on the results is large, as the incremental cost is reduced by 44% to £1,849 and the incremental QALY increases to 0.038 (+61%).

- Similar situation for re-hospitalization, with a reduced HR for the 1st year (HR=0.73), and beyond, the opposite with an increased HR = 1.91 used in the NICE model – based on the same RCTs compilation. From the PARTNER 3 trial, the 1-year and 2-years re-hospitalization hazard ratios are much lower with HR = 0.63 and HR = 0.67 respectively. From the latest 5-years data from the PARTNER 3 trial, the overall HR for re-hospitalization is 0.75 – quite far from the 1.91 used in the NICE model.

- When combining all short-term and long-term assumptions from the PARTNER 3 trials as described above, the results change completely, and TAVI with SAPIEN 3 becomes highly cost-effective.

Events	NICE (TAVI/SAVR)	PARTNER 3 (TAVI/SAVR)	Δ Cost	Δ QALY	ICER
NICE Base Case			**+ £ 3 300**	**+ 0.024**	**£ 139.8k**
Conv. SAVR	0.55% / NA	0.2%	+ £ 3 287	+ 0.029	£ 113.1k
Mod/Sev PVL	2.7% / 0.2%	0.8% / 0.0%	+ £ 3 300	**+ 0.04**	**£ 77.3k**
Stroke	2.1% / 2.5%	0.6% / 2.4%	**+ £ 2 401**	**+ 0.051**	**£ 47.1k**
Bleeding	2.3% / 9.4%	1.2% / 11.9%	+ £ 3 301	+ 0.03	£ 127.5k
Pacemaker	9.7% / 5.4%	6.6% / 4.1%	+ £ 3 321	+ 0.03	£ 122.4k
Mortality	0.6% / 0.7%	0.4% / 1.1%	+ £ 3 160	+ 0.027	£ 117.3k
Utility Extrap.			+ £ 3 300	+ 0.026	£ 125.0k
LT Mortality @ 1y/2y	HR=0.91/0.97	General population mortality w. HR = 0.41 / 0.75	+ £ 3 692	**+ 0.187**	**£ 19 738**
AV re-interv.	HR = 1.87	HR = 1	**+ £ 1 849**	**+ 0.038**	**£ 49.2k**
Re-hosp. @1y / 2y	HR = 0.73/1.91	HR = 0.63 / 0.67	+ £ 2 708	+ 0.024	£ 114.7k
Combined Effect			**+ £ 394**	**+ 0.24**	**£ 1 617**

Appendix [B3]: 30-days mortality estimates from RWE data comparing TAVI and SAVR

Title	Study type	Year	Mortality (TAVI vs SAVR)	Source
Comparison of Outcomes After Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Among Patients with Aortic Stenosis at Low Operative Risk	Propensity score-matched analysis (of RWE) data from Finnish Registry primary outcomes were 30-day and 3-year survival	2008 – 2017 Finland	30-day mortality: 1.3% with TAVI and 3.6% with SAVR Not significant: p = .12	[1]
Mortality in low-risk patients with aortic stenosis undergoing transcatheter or surgical aortic valve replacement: a reconstructed individual patient data meta-analysis	Meta analysis. Includes the above 3 studies as well as RCT studies (PARTNER 3, EVOLUT, NOTION). "all published (above) studies lacked statistical power to detect differences in individual outcomes between TAVI and SAVR"	Studies of varying lengths ranged from 2009 - 2018	30-day mortality: 1.1% TAVI vs 1.8% SAVR HR 0.59, 95% CI 0.35–0.99; P = 0.048	[2]
Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results	Propensity score-matched analysis (of RWE)	2014 – 2015 Germany	30-day survival: 98.1% TAVI and 97.1% SAVR, P = 0.014	[3]

from the German Aortic Valve Registry (GARY)				
Outcomes of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients	Meta-analysis of 4 RCTs (PARTNER 3, SURTAVI, EVOLUT, NOTION)	2018 – 2019	30-day mortality: 0.7% TAVI and 1.9% SAVR, OR 0.46 (95% CI 0.22–0.97), P = 0.04	[4]
Cardiovascular Outcomes with Transcatheter vs. Surgical Aortic Valve Replacement in Low-Risk Patients: An Updated Meta-Analysis of Randomized Controlled Trials	Meta-analysis of 5 RCTs (PARTNER 3, SURTAVI, EVOLUT, NOTION, STACCATO)	2012 – 2019	30-day mortality: 0.8% TAVI and 1.4% SAVR, OR 0.51 (95% CI 0.24–1.11), P = 0.09	[5]
Meta-analysis of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Patients with Low Surgical Risk	Meta-analysis including 12 studies, 5 RCTs and 7 observational studies	2012 – 2019	30-day mortality: 1.7% TAVI and 2.7% SAVR, OR 0.66 (95% CI 0.55–0.80), P < 0.0001	[6]
Meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients at low surgical risk patients:	Meta-analysis including 9 studies, 4 RCTs and 5 observational studies with propensity score matching (PSM)	2012 – 2019	30-day mortality: 1.4% TAVI and 2.1% SAVR, OR 0.68 (95% CI 0.46–1.00), P = 0.05	[7]
Transcatheter versus surgical aortic valve replacement in low surgical risk patients: A meta-analysis of randomized-controlled trials and propensity-matched studies	Meta-analysis including 10 studies, 5 RCTs and 5 observational studies with propensity score matching (PSM)	2012 – 2019	30-day mortality: 1.8% TAVI and 2.8% SAVR, OR 0.67 (95% CI 0.56–0.80), P < 0.001	[8]

[1] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2735762
[2] https://pubmed.ncbi.nlm.nih.gov/32995837/
[3] https://pubmed.ncbi.nlm.nih.gov/30445543/
[4] https://www.heartlungcirc.org/article/S1443-9506(20)30099-8/abstract
[5] https://www.sciencedirect.com/science/article/abs/pii/S1553838919304828?via%3Dihub
[6] https://www.sciencedirect.com/science/article/abs/pii/S0002914919312226
[7] https://www.sciencedirect.com/science/article/abs/pii/S0002914919312226
[8] https://www.sciencedirect.com/science/article/abs/pii/S1553838919306414

NICE response to resolution request 2

Following review, the NICE team considers part of this resolution request relating to the cross-referencing of NG208 in the guidance to contain potential grounds for resolution on breach of process. This issue will be discussed at the panel meeting.

The team does not believe that the remainder of the request constitutes grounds for resolution on factual errors or breach of process, and the response to these points is presented here:

The conclusion that NG208 is a valid piece of guidance that remains relevant was reached by the committee and represents its own view. Conflicting scientific or clinical interpretations or judgements are not considered to be factual errors. The committee was not tasked with re-assessing the value of TAVI compared with surgery. The company was given the opportunity to comment during consultation on NG208 and took part in that process at the time, including commenting on the model which was made available to stakeholders on request. Further potential issues raised by the company in this request and the attached Appendix relating to the NG208 assessment have been passed on to NICE's Guidelines Surveillance team.

The company claims that section 1.3 of the guidance (Value for money should be determined considering the cost-effective price for transcatheter heart valves described in NICE's guideline on heart valve disease) is factually inaccurate. This statement is a committee recommendation - conflicting scientific or clinical interpretations or judgements are not considered to be factual errors.

The company claims that the reference to the cost of £14,800 in the 'What this means in practice' section is factually inaccurate. The aim of this LSA was to assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation devices […] to inform procurement decisions. Determination of a cost-effective price for a generic TAVI valve was beyond the remit of the late-stage assessment, so cost-effectiveness prices identified in NICE's guideline on Heart valve disease (NG208) were provided for context in the final guidance. Following review, the NICE team does not consider this to be a factual inaccuracy that impacts the conclusions of the committee.

However NICE accepts that further granularity in the information provided would be useful. NICE agrees that NG208 found that a valve would have to cost £14,800 only in the case that all people having TAVI are at low surgical risk. Therefore, NICE will amend the wording to:

- "But, the valve would have to cost £14,800 or less for TAVI to be cost effective for people **who are at low surgical risk.**

Evidence was not generalised for licenced indications to products outside that indication (see response to resolution request 1).

Appendix C: Letter from Edwards Lifesciences 04/02/2025

Re: NICE Late-stage assessment guidance: Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis

Dear Sarah,

I write in response to your letter dated 24 January 2025, providing NICE's initial scrutiny of our resolution requests in respect of the late-stage assessment ("LSA") cited above. We are grateful for your initial scrutiny letter and confirmation that elements of two of the resolution requests we raised under Ground 1 (breach of NICE's published process for the development of guidance) will be put before the resolution panel. We have received the proposed Briefing Paper and will provide our comments in due course. However, we are disappointed to see several of our resolution requests dismissed before due consideration by a resolution panel. For the reasons below, we request that NICE reconsiders its position.

Request for Further Scrutiny and Reconsideration

NICE unfairly rejected several of our resolution requests based on the view that the relevant issues represent differences of scientific opinion, rather than factual errors or breach of process. However, merely stating that the LSA committee reached its own conclusion based on what was presented to it, does not meet the requisite standard of transparency for NICE appraisals, and therefore represents a breach of process. Further, NICE's reliance on this

argument does not address the clear dismissal of key relevant evidence and mistaken assumptions that underly several of the committee's conclusions. For example:

- NICE accepts in its response to Resolution Request 1 that ignoring key evidence consistent with the scope and decision problem "*has the potential to lead to factual inaccuracies* ***if such evidence exists***" (emphasis added). Edwards presented evidence to NICE which considers TAVI devices fairly, accurately and in large numbers, – demonstrating that such evidence does exist. Please see appendix [C2] for details. Among other reasons, this evidence has been deemed to be either out of scope, or 'in scope but not key evidence', on the grounds of making comparisons against surgery, including older generation devices, mixing interventional approaches and on the grounds of non-UK data (all of which were prevalent in the development of the original NG208 economic model). Edwards and others also presented evidence to NICE which had not been captured using pragmatic searches and this was included in the Addendum.
- NICE also failed to provide visibility or opportunity to comment on the extensive External Assessment Report Addendum detailing the reasons for the determination of "not key evidence" of certain clinical data. The reasoning given in this document, which was sent to us on request on 30 January 2025, represents a clear case of double standards with regard to "scientific opinion" on which evidence is relevant, given that the justification for rejecting evidence in many cases also applies to NG208 (on which the committee heavily, and unfairly, relied). The failure to distribute such material evidence is also a clear breach of NICE's Health Technology Evaluations Manual (specifically, Sections 5.8.67 and 5.8.69) and this should be included for discussion in the resolution panel meeting. The breach did not come to light until long after the deadline for the submission of resolution requests in December 2024.

- In any event, NICE's failure to consider this evidence resulted in factual inaccuracies (as NICE admits is a possibility, see above) and the committee forming its conclusions on the basis of erroneous assumptions. Accordingly, NICE cannot rely on the inadequate "difference of scientific opinion" basis provided at various points in the initial scrutiny letter, such as in response to Resolution Requests 3, 7, 12, 14 and 20, to dismiss substantive points prior to consideration by the resolution panel. We therefore request that these be duly presented to the resolution panel.

Further, in the response to Resolution Request 1, the initial scrutiny letter refers to "additional steps" that NICE included in the process for this LSA following scoping to "*ensure that the assessment was as robust as possible and that no relevant evidence was missed*." These steps included providing opportunities for stakeholders to submit evidence and permitting the External Assessment Group time to "*review the submitted evidence and produce an addendum to the assessment report*" (cited above). However, such steps do not represent supplementary concessions to stakeholders, but rather were essential for NICE to uphold the standards of fairness and transparency which its processes demand (although, irrespective of these steps, NICE ultimately fell short in this LSA).

NICE's initial scrutiny letter fails to address the point we raised under Resolution Request 2 with respect to transparency and the clear breach of process related to the use of NG208 in making a recommendation on technology pricing. As stated in the Resolution Request, given that the committee placed substantial weight on the original NG208 model in reaching its decision, a fully executable version of that model should have been offered during consultation (a point also confirmed by the Court of Appeal). In stark contrast, NG208 was opaquely introduced in the closed section of the first committee meeting, leaving stakeholders in the dark as to how the committee considered it. It is imperative that this lack of transparency and self-evident

undermining of NICE's processes be presented for consideration by the resolution panel.

NICE also states in response to Resolution Request 2 that "*cost-effectiveness prices identified in NICE's guideline on Heart valve disease (NG208) were provided **for context** in the final guidance. Following review, the NICE team does not consider this to be a factual inaccuracy that impacts the conclusions of the committee*." NICE appears to accept that the use of NG208 led to factual inaccuracy but suggests that this did not impact the committee's conclusions. The draft guidance makes clear that NG208 had substantial influence over the committee's decisions, so the factual inaccuracy cited here must be presented for consideration by the resolution panel.

We also note that the appendix containing extensive details of where the factual inaccuracies in the original NG208 calculations has been passed on to NICE's Guidelines Surveillance team, however, this contained clear examples of major flaws in its logic and conclusions which do not appear to have been taken into account in this initial scrutiny.

Further, NICE's initial scrutiny letter rejects the points we raised in Resolution Requests 1 and 2 regarding the LSA generalizing evidence for licensed indications to products outside such indications. In its response to Resolution Request 1, NICE states that "*[all NICE HealthTech guidance implicitly includes the provision that the product should be used within its intended use in line with UKCA or CE marking, and only if it is explicitly to be used off-label would this be stated*." The implication seems to be that, unless a technology is explicitly contra-indicated for a particular use/population, it can be seen as indicated for that use/population. This is self-evidently a flawed assumption and, as such, NICE's reasoning here is insufficient for dismissing these elements of Resolutions Requests 1 and 2 prior to consideration by the resolution panel.

With respect to NICE's calculation of net monetary benefit ("NMB"), the External Assessment Group demonstrated that SAPIEN 3 had the highest

probability of having the highest NMB (without any overlap of the confidence intervals), but NICE unfairly determined this too uncertain to report. NICE's initial scrutiny letter rejects Resolution Requests 3 and 24 on this basis, citing the overlapping NMB confidence intervals. As we set out in Resolution Request 14, the drastically unbalanced patient sample sizes between the TAVI devices considered in this LSA significantly impacted quality-adjusted life years ("QALYs") variability, which in turn contributed to the overlapping NMB confidence intervals. Given this clear explanation for the overlapping NMB confidence intervals, it is inadequate to simply reject our resolution requests on this point citing uncertainty, particularly given that SAPIEN 3 stood out as having a substantially and statistically significantly higher probability of having the highest NMB of all devices – for both the male and female models. At the least, therefore, these points should be presented for consideration by the resolution panel. To dismiss them at this stage without adequate explanation falls far short of the standards of fairness expected of NICE.

Linked to the above, NICE's initial scrutiny letter also rejects Resolution Request 14, which stated that the committee's finding of robust linkage between the UK TAVI registry and hospital episode statistics data was inaccurate. NICE rejected this Resolution Request on the grounds that we outlined the limitations of the UK TAVI registry data in the Resolution Request, rather than the linkage process. This does not add up as a reason for dismissing our Resolution Request. We highlighted the limitations of the data to demonstrate the implications of the lack of robust linkage. This is not merely a difference in scientific opinion, as NICE suggests. The committee has based its conclusions on incorrect assumptions and failed to provide transparent justification for doing so. Accordingly, we request that NICE presents Resolution Request 14 to the resolution panel for discussion.

We look forward to discussing these points at the resolution panel meeting, and request that you kindly confirm that the resolution requests noted in this letter will be presented in their entirety to the resolution panel.

Yours Sincerely,

Jeff Stonadge

Director Market Access and Government Affairs

Appendix [C2]

Study name	How / when first brought to NICE attention	Assessed by EAG in V6 EAR report? Yes / No	Response from NICE to reference supplied in draft guidance comments Yes / No	Reviewed in the addendum Yes / No	Outcome and reason given	NICE Comment
Clinical Evidence Comparing TAVI devices						
Senguttuvan et al., 2023	Letter 31.10.23; Edwards RFI submission	N	Y	Y	In scope, not prioritised: included older generation devices in the intervention arm or comparator arm or both	
Godzek et al., 2020	Letter 31.10.23; Edwards RFI submission	N		Y	In scope, not prioritised: included older generation devices in the intervention arm or comparator arm or both	
Takagi, et.al. 2019	Letter 31.10.23; Edwards RFI submission	Y			In Scope but not Key Evidence	Included in main text of EAR
Van Belle, et.al. 2020	First draft guidance consultation*	N	N	N	In scope, not prioritised due to older generation devices in the intervention arm or comparator arm or both	Included in addendum

Beyersdorf, et.al. 2021	First draft guidance consultation*	N	N	Y	Excluded: comparison with SAVR	
Attinger-Toller, et.al. 2021	First draft guidance consultation*	N	N	Y	Excluded: compared outcomes by age group	
Deharo, et.al. 2020	First draft guidance consultation*	N	Y	Y	Included in addendum	
Guerreiro, et.al. 2020.	First draft guidance consultation*	N	N	Y	Excluded: compared transfemoral and nontransfemoral access routes	
Durand, et.al. 2020	First draft guidance consultation*	N	N	Y	In-scope, not prioritised due to older generation devices in the intervention arm or comparator arm or both	EAG included Durand 2021 but not Durand 2020. Both evaluate length of stay after TAVI but only the 2021 analysis compares different models of valve. The 2020 study is a single arm trial of SAPIEN 3 only.
Okuno et. al. 2023	First draft guidance consultation*	N	N	Y	In-scope, not prioritised due to older generation devices in the intervention arm or comparator arm or both	
Lanz et al., 2019	Letter 14.02.24	N	N	Y	In scope, not prioritised: included older generation devices in the intervention arm or comparator arm or both	

Linke et al., 2017	Letter 14.02.24	N	N	N		Study is included in the systematic review Senguttuvan et al. 2023 which is included in the addendum
Makkar et al., 2020	Letter 14.02.24	N	N	Y	In Scope not prioritised : combined TAVI devices from different manufacturers in the comparator arm	
Durand et al., 2021	Letter 14.02.24	N	N	Y	In-scope, not prioritised due to older generation devices in the intervention arm or comparator arm or both	
D'Ascenzo et al., 2021	Letter 14.02.24	N	N	Y	In Scope not prioritised: combined TAVI devices from different manufacturers in the comparator arm	
Li et al., 2020	Letter 14.02.24	N	N	Y	In Scope not prioritised compared different generation devices from the same manufacturer against each other	
Al-Abcha et al., 2021	Letter 14.02.24				In Scope but not Key Evidence	Included in EAR.
Rheude et al., 2021	Letter 14.02.24	N	N	Y	Not in Scope	

Schofer, et.al. 2022	First draft guidance consultation*	N	N	Y	Excluded: compared outcomes between different surgical risk categories	
Jørgensen, et.al. 2021	First draft guidance consultation*	N	N	Y	Excluded: compared TAVI with SAVR	
Tarantini, et.al 2021	First draft guidance consultation*	N			Tarantini 2022, Accurate Neo study excluded due to Outcomes: Commissural and coronary alignment with postprocedural computed tomography.	Included in the Addendum
Clinical Evidence Specific to SAPIEN 3 Ultra						
Welle, G.A., et al.2021	First draft guidance consultation*	N	Y	Y	Review of draft guidance consultation states: Not of higher quality, or more relevant, evidence than that already summarised in the EAG report. ** Addendum states: In scope, not prioritised: compared SAPIEN 3 Ultra with	

					SAPIEN 3.	
Nazif et al., 2021	First draft guidance consultation*	N	Y	Y	In scope, not prioritised compared different generation devices from the same manufacturer against each other	
Saia et al., 2020	First draft guidance consultation*	N	Y		Excluded: not of higher quality, or more relevant, evidence than that already summarised in the EAG report.**	Study was notified at EAR comment phase and EAG responded, so was not prioritised for reassessment in addendum.
Rheude et al., 2020	First draft guidance consultation*	N	Y	N	Excluded : not of higher quality, or more relevant, evidence than that already summarised in the EAG report. **	Study was notified at EAR comment phase and EAG responded, so was not prioritised for reassessment in addendum.
Economic Evidence - Peer Review						
Goodall G et al., 2020	Letter 31.10.23;	N	N	N	No response	Included in EAR, Goodall 2019
Gilard et al., 2022	Letter 31.10.23	Y			Used to validate the model structure ONLY	NICE note that economic evaluations of TAVI vs SAVR did not address the decision question and so were not reviewed outside of validating the bespoke model for this assessment.
Lorenzoni V et al., 2021	Letter 31.10.23	Y			Used to validate the model structure ONLY	

Pinar et al 2022	Letter 31.10.23	N	N	N	No response	Included in EAR, mistakenly reported as Pinar 2021
Mennini et al. 2022 (Italy)	Letter 31.10.23; Edwards RFI submission	N	N	N	No response	For this study and the others below up to Kobayashi et al, the EAG responded at EAR consultation, stating “The EAG has reviewed the title and abstract of the references, all compare TAVI and SAVR, none in a UK setting; therefore unlikely to change the summary of the EAG report.”
Vázquez Rodríguez et al. 2023 (Spain)	First draft guidance consultation*	N	N	N	No response	See above
Kuck et al. 2023 (Germany)	Letter 31.10.23; Edwards RFI submission	N	N	N	No response	See above
Galper et al. 2023 (USA)	First draft guidance consultation*	N	N	N	No response	See above
Tchétché et al. 2023 (France)	First draft guidance consultation*	N	N	N	No response	See above
Dubois et al. 2023 (Belgium)	Letter 31.10.23; Edwards RFI submission	N	N	N	No response	See above

Eerdekens et al. 2024 (Netherlands)	First draft guidance consultation*	N	N	N	No response	See above
Kobayashi et al. 2024 (Japan)	First draft guidance consultation*	N	N	N	No response	See above
Zhou JY et al., 2021	Letter 31.10.23	Y			Used to validate the model structure ONLY	
Tam DY et al., 2020	Letter 31.10.23	Y			Used to validate the model structure ONLY	
Tarride JE et al., 2019	Letter 31.10.23	Y			Used to validate the model structure ONLY	
Heathcote L et al., 2023	Letter 31.10.23; Edwards RFI submission	Y			Used to validate the model structure ONLY	

* Key evidence brought to the attention of NICE / the External Assessment Group which had not been identified in the original External Assessment Report search, or previously submitted by Edwards.

** Following consultation comments EAG has reviewed the titles and abstracts only, per External Assessment Report, User Preference Report and economic model – Collated comments

NICE National Institute for Health and Care Excellence

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation to treat aortic stenosis: late-stage assessment

EAR Addendum 2 - Factual accuracy check collated comments

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG response
1	Stakeholder 1 Medtronic	7	1	We question whether this addendum 2 sufficiently addresses the resolution panel's request to **"review the approach to searching for and selecting evidence".** The stated aim of this addendum is ***"to support the committee in this discussion by conducting a systematic search of published literature directly inter-comparing the clinical effectiveness of TAVI devices used in the treatment of aortic stenosis, and to summarise any new relevant evidence that has been published since the original External Assessment Group (EAG) report was submitted"***. The systemic literature review starting from 2022 may have missed a significant body of evidence published prior to this date. For comparison, NG2308: *Heart valve disease presenting in adults: investigation and management*, applied date filters as follows: Medline: 1946-2020 and Embase: 1974 – 2020 (search strategy 8,	Thank you for your comment. This is not a factual inaccuracy. The EAG have conducted several searches for this Late Stage Assessment including the initial searches for the original EAG Report which included published evidence from 01 January 2020 (Appendix A, original EAG Report) to capture any evidence published since the searches for NG208 (conducted in October 2020, capturing records from 1946 to 14 October 2020, NG208 Search Strategies A.1). The start date for the searches supporting Addendum 2 report was 1 January 2022 based on the systematic review by Yang et al. 2023, which was included in the original EAG Report and included evidence from databases inceptions up to 1 February 2022. This ensures coverage of the literature. The updated literature search included systematic reviews of previously published studies, together with RCTs, and targeted

				https://www.nice.org.uk/guidance/ng208/documents/search-strategies). We accept that a limited evidence review was a pragmatic approach, given this is the resolution stage of the process, and we do not expect a full systematic review at this stage however we ask the committee to note this limitation which significantly limits the ability to draw conclusions regarding the suitability of the RCT data to address the decision problem.	device evidence as appropriate. Across the searches conducted and through three consultation processes the EAG has reviewed more than 300 full papers. The consultee has challenged the pragmatic literature search approach by the EAG but has not specified any specific study that was missed by the EAG that would be considered pivotal to the decision problem. Therefore, no changes have been made to Addendum 2 to address this comment.
2	Stakeholder 1 Medtronic	34	Para 2	***"Taking into account both sources of information, the EAG consider that analysis of 6,267 patients from the UK TAVI Registry has more suitable data generalisable to a UK population".*** The statement that the analysis included 6,276 patients from the UK TAVI registry is factually incorrect as only 3,917 (62% of the 6,270) had complete data available and could contribute to the multivariate analysis (EAR Report: GID-HTE10027 TAVI LSA Report v5, page 11).	Thank you for your comment. To clarify, a total of 6,267 patients from the UK TAVI registry were analysed in univariable analysis (see Table 20, Table 21 and Table 22 of the original EAG report), and a subset of 3,917 patients with complete data for the mortality outcome were incorporated in multivariable analysis. Therefore, the text has been amended to "the EAG consider that univariable analysis of 6,267 patients (multivariable analysis conducted in a subset of 3,917 patients with complete data) from…" to make this clear to Committee.

3	Stakeholder 1 Medtronic	12	Para 3	*The EAG correctly state that the ACURATE neo2 valve has been removed from the market globally but it is not clear that this decision was made following results from a randomised controlled trial whereby the valve failed to demonstrate non-inferiority versus SAPIEN 3 and Evolut. We would therefore like to highlight the attached study to the EAG:* ***ACURATE neo2 valve versus commercially available transcatheter heart valves in patients with severe aortic stenosis (ACURATE IDE): a multicentre, randomised, controlled, non-inferiority trial.*** *Lancet 2025; 405: 2061–74, published online May 2025. The publication just missed their cut-off date of 11th April 25.* *Added value of this RCT as described by the authors: ACURATE IDE is the largest randomised head-to-head comparison of TAVR platforms to date, comparing the safety and efficacy of the ACURATE neo2 valve versus SAPIEN 3 and Evolut valves in patients with symptomatic severe aortic stenosis across a spectrum of surgical risk. This trial found that ACURATE neo2 did not reach non-inferiority for the primary composite endpoint of all-cause mortality, all stroke, and rehospitalisation at 1 year compared with the control valves, SAPIEN 3 and Evolut. Patients in the ACURATE neo2 group had significantly higher rates of cardiovascular mortality, stroke, rehospitalisation, unplanned use of cardiopulmonary bypass, and lower device success than patients in the control group.*	Thank you for your comment. This is not a factual inaccuracy. The EAG note that the ACURATE IDE non-inferiority trial was published after the EAG conducted their updated searches for Addendum 2; therefore was not missed by the literature searches conducted. This trial randomised patients to ACURATE neo2 (device now withdrawn from market) or a control group of patients receiving either a Medtronic Evolut device (R, Pro, Pro+, or FX) or Edwards Lifesciences Sapien 3 or Sapien 3 Ultra device with statistical analysis reported between the ACURATE Neo2 recipients and the control group (block randomisation stratified by clinical investigation site and type of control valve used). The study recruited 752 and to the intervention arm and 748 patients to the control arm (n=504 Edwards Lifesciences; n=244 Medtronic) across 71 sites in the US and Canada. The primary endpoint was a composite of all-cause mortality, all stroke and rehospitalisation at 1 year, tested for non-inferiority using a Bayesian approach with a non-inferiority margin of 8%. The EAG note that no statistical analyses were conducted (at a manufacturer or device level) within the control group and the study was not powered to detect differences between devices in the control arm. Furthermore, as the ACURATE neo2 has been withdrawn from market this additional study would not alter the

				Echocardiographic assessments showed that, although the ACURATE neo2 valve provided favourable haemodynamic performance, it was associated with higher rates of prosthetic valve regurgitation. These findings provide robust evidence of the device's limitations in clinical performance compared with established platforms. This study is very relevant to the LSA as it demonstrates that differences in clinical outcomes exist between TAVI devices and reinforces the need for new TAVI valve platforms to have RCT data before widespread patient access is granted to patients.	conclusions within the EAG Report or corresponding Addenda. The EAG note that conduction of a randomised controlled trial relies on clinical equipoise and agree that robust evidence is required to support the use of technology available to patients. No changes have been made to Addendum 2 to address this comment.
4	Stakeholder 1 Medtronic	38	5	*"Significantly fewer strokes at 5 years were also found with Evolut R compared to Sapien 3 but when stratified by annular dimension* ***this finding only held for those with an annular diameter less than or equal to 430mm2*** *(defined as small annulus)"*. We suggest this statement minimises this study outcome and ask the EAG to note that a significant proportion of the patient population met the definition of "small annulus". Where significance is demonstrated, it is for the full study population.	Thank you for your comment. This is not a factual inaccuracy. Feistritzer et al. (2025) reported a significant difference for the full study population and "*An analysis stratified by annular dimensions showed that stroke rates differed between SEV and BEV only in patients with a small aortic annulus (≤430 mm^2), but not in those with an annulus >430 mm^2*". The total number of patients who would be defined as having a small annulus is not explicitly defined in this paper but from the percentages reported in the Feistritzer et al. 2025 supplementary tables the EAG note that approximately 50% of the cohort would have been considered to have small annulus. We have added this to the Addendum 2 report for context.

5	Stakeholder 1 Medtronic	42	6	The EAG concludes that the key limitations described in the original EAG report remain, including: ***"no randomised evidence was generated from a UK NHS setting".*** Whilst evidence generated from a UK NHS setting is preferred for economic evaluations, there is no requirement in NICE Methods for UK evidence on clinical effectiveness therefore we disagree that this is a key limitation. We suggest it is unrealistic for the EAG to expect UK specific RCTs and HTA bodies globally do not require country specific data. We ask the EAG to note that the RCTs included meet the population scope and that the SMART trial[1] has UK patients. Herrmann H, et al. Rationale and Design of the Small Annuli Randomized to Evolut™ or SAPIEN™ Trial (SMART Trial) American Heart Journal (2021), doi: https://doi.org/10.1016/j.ahj.2021.09.011	Thank you for your comment. This is not a factual inaccuracy. The EAG have summarised the published clinical evidence regardless of setting. The SMART trial as reported by Herrmann et al (2024) was included in the original EAG report. This trial reported 83 sites across 13 countries, where 36/716 (5%) patients were from the UK, but no sub-analysis was done by country. The EAG consider that results within a UK NHS setting will be more generalisable to this decision problem when accounting for differences in healthcare provision and populations (such as, treatment eligibility or discharge pathways) in other countries. Therefore, no changes have been made to Addendum 2 to address this comment.
6	Stakeholder 2 Edwards Lifesciences		General	We have sought to focus on factual accuracy in this response. However, in a number of areas these points impact on broader issues that the committee will need to discuss. Where appropriate, we have tied factual accuracy to points of discussion that impact on decision making.	Thank you for your comment. No changes have been made to Addendum 2 to address this comment.
7	Stakeholder 2 Edwards Lifesciences	7	2.1	We note that only one reviewer conducted the full literature search, which is at odds with NICE's own methods manual	Thank you for your comment. This is not a factual inaccuracy.

				https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741) section 3.4.5, which states "More than 1 reviewer should assess all records retrieved by the search strategy to increase the validity of the decision." Accepted standard reviewing practice should involve at least two reviewers assessing all records, as referenced in the One-piece closed bag for adults with colostomy LSA report EAG protocol. (https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf) In this addendum, a small sample (10%) was checked by a second reviewer. Only 0.3% of the evidence identified (10 out of the 3,199 extracts) has then been considered with respect to the decision problem. This is a surprisingly small figure given that the initial EAG report comments on the large volume of evidence for this topic.	The EAG assume that the consultee is referring to the total number of titles and abstracts identified from the searches prior to deduplication (3,199) and the 10 studies included within the main Addendum (excluding the deprioritised studies summarised in Addendum Appendix D). To clarify, the sift of 2,368 titles and abstracts after de-duplication (466 records from identification of systematic reviews, 1,824 RCTs, and 78 additional from targeted searches) as described in the PRISMA diagram in Appendix D was conducted by a single reviewer (and 10% sample underwent QA by a second reviewer which included 47/466 systematic reviews, 183/1,824 RCTs, 9/78 additional targeted searches). The EAG confirm that all included full papers were also reviewed by a second reviewer, additionally all reasons for exclusion were also QAd by a second reviewer. No changes have been made to Addendum 2 to address this comment.
8	Stakeholder 2 Edwards Lifesciences	12 and 27	4.5.6	One example that illustrates the concerns we have noted above relating to the thoroughness and accuracy of the literature search, is the non-inclusion of the 2024 TCT abstract illustrating the ACURATE Neo 2 IDE trial (https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2024/10/29/03/43/acurate-ide). This critical evidence, which was notified by separate communication to NICE on	Thank you for your comment. This is not a factual inaccuracy. As described in eligibility criteria (section 2.2) the EAG excluded conference abstracts within the updated searches for Addendum 2. The EAG note that the abstract highlighted by the consultee was published after submission of the EAG Report and Addendum 1, and the full publication was also published after

				November 1st 2024, reports a failure to demonstrate non-inferiority of the ACURATE Neo 2 TAVI device in an independent oversight and long-term follow-up RCT trial (per FDA requirements). This was actually the 3rd non-inferiority trial of that device that failed, following on from the previous SCOPE I and SCOPE II trials. The full publication was published May 21 2025 in the Lancet and directly led to the discontinuation of the TAVI device and the quoted press release on page 12 of the addendum. The importance of this is that it shows that the industry itself looks closely at the differences between products that justify price variation and even whether it is worth products entering the market at all. If the industry is capable of making its own such distinction between products, then it is surely incumbent upon NICE to do so.	submission of the EAG Addendum 2 (where the searches were conducted on 11 April 2025). See response to comment #3 where the limitations of the IDE trial have been outlined. The EAG note that there is no published evidence for all device comparisons possible between the devices listed in the NICE Final scope (see Figure 1 for comparisons included in Addendum 2). No changes have been made to Addendum 2 to address this comment.
9	Stakeholder 2 Edwards Lifesciences			In leading the committee to the conclusion that the published data is not useful to the decision problem, the EAG did not comply with all of the instructions of the resolution panel. They have effectively taken the committee's role to "review the approach to (searching for and) selecting evidence in this LSA" rather than providing options to the committee in order that they can take that decision.	Thank you for your comment. This is not a factual inaccuracy. The EAG have been commissioned to independently synthesise the available evidence about the clinical effectiveness and value for money of the technologies and present these findings to committee as per the NICE health technology evaluation Methods Guide (PMG36) and Late Stage Assessment

				Experts in the committee have previously said that non-UK trials are generalisable to UK practice and have stated, in comments on the initial draft guidance, that they believe that there is sufficient published evidence from which conclusions can be drawn. The concern highlighted by the resolution panel was that the EAG did not fully explore the existing evidence. We would submit that this same faulty approach has been adopted here. The addendum actually does show that it is possible to make comparisons from the published literature. It makes the correct statement that "Economic models comparing different TAVI valves requires consideration of relevant clinical outcomes (as defined by VARC) including: death, stroke, major or severe paravalvular leak, pacemaker implantation, subsequent TAVI or SAVR intervention, all of which can occur in-hospital or longer-term." The EAG has failed to summarize the consistently similar evidence in the studies that it considered to be relevant to the decision problem. Despite limitations identified in the literature search, there is a clear significant difference seen among the various TAVI devices, as illustrated in bold text in Annex 1. (supplied below). Indeed, in most of the studies considered, the SAPIEN 3 device (incl. S3U) reduces the moderate/severe PVL incidence at least 2-fold and reduces the need for a permanent pacemaker by at least 30%. Both	Interim Process and Methods Statement. The EAG have summarised the data from clinical and real-world evidence sources relevant to the decision problem within the Report and Addendums including the respective limitations of each data source and have provided justification for the approaches used. Whilst the consultee has challenged the approach, no specific evidence has been identified as missing. Furthermore, the EAG notes that the table supplied in Annex 1 summarises the existing evidence captured within Addendum 2 with the addition of 2 studies that were published after the EAG searches: • Makkar et al. 2025, please see response to comment #3 where the limitations of the IDE trial have been outlined • Tavakoli et al. 2025, the prospectively registered meta-analysis (CRD42024541236) compares outcomes between balloon-expanding and self-expanding TAVI devices short-term (up to 30 days), mid-term (1 year) and long-term (beyond 1 year). The meta-analysis included 10 RCTs reported in 18 publications; this aggregated different TAVI valves in both intervention and comparator arms and included older generation of TAVI devices which were not listed in the Final Scope. The supporting supplementary manuscript provides statistical analysis for several outcomes between older and newer generation devices (manufacturer and device not reported) and between four

				clinical outcomes are associated with long-term mortality and quality of life, impacting the QALY gained. This convergence is less pronounced with mortality and stroke, but there is clearly a trend in that direction. The evidence seen in the second addendum supports the first EAG report finding (comparing the six valves with data) that SAPIEN 3 has the highest probability of delivering the highest net monetary benefit.	older generation devices (CoreValve, Evolut, ACURATE, and Portico). All trials have been considered within the EAG Report and corresponding Addenda (either included or excluded with reason). The EAG note that the outcomes were reported for older generations and not between specific devices in Scope of this assessment. As these publications do not add evidence that would change the EAG approach or conclusions for this topic, no changes have been made to Addendum 2 to address this comment. The EAG note that the real-world evidence from a UK NHS setting confirms some of the trends identified in the literature (see Table 23 of the original EAG report where higher event rates of stroke, AR, pacemaker were seen for some valves in multivariable analysis when compared to Sapien 3 Ultra as the reference). The EAG note (as stated in the original EAG report) that Sapien 3 had the largest probability of the highest NMB at £20,000 willingness to pay threshold. As also stated in the original EAG report, this was a consequence of these valves being used more frequently, therefore more prevalence in the UK TAVI Registry data, leading to narrower confidence intervals for the inputs of the economic model.

					Therefore, no changes have been made to Addendum 2 to address this comment.
10	Stakeholder 2 Edwards Lifesciences			To state that the UK TAVI registry linked to HES data is a better source of evidence than published clinical data, to assess evidence to justify price variation between the TAVI devices in the scope of this LSA, is factually incorrect. Half of the available technologies remaining in the scope of the LSA have no data upon which any decision can be made. For those with data captured, the NICOR registry was never set up to make inter-device comparison and it has major limitations in capturing key outcomes that would have major economic impact. NICE cannot draw conclusions based on the relative cost-effectiveness of TAVI devices at various levels of surgical risk – as implied in the final draft guidance - using the registry, because surgical risk level is not captured. (See P.11 of the first EAG report v5)	Thank you for your comment. This is not a factual inaccuracy. The EAG has not stated that the real-world evidence was “better”. The EAG have summarised the available published clinical evidence for the technologies included within the Scope of this NICE evaluation in addition to conducting analysis of the available real-world evidence within a UK NHS setting (Hospital Episode Statistics and UK TAVI Registry data). The EAG have summarised the key limitations for the use of both published clinical evidence and real-world evidence from the UK TAVI Registry within the EAG Report (Executive Summary, Tables 4 and 5, Sections 5.2-5.6) and Addendum 2 (Section 6). The EAG have outlined their consideration of all information sources and have provided justification for the view that the real-world evidence from the UK TAVI Registry presents data more generalisable to the decision problem about device performance within the UK NHS. The EAG have acknowledged the availability of evidence (including published and real-world evidence) differs between the technologies included within the NICE Final Scope. Evidence gaps have been highlighted in the original EAG report (section 7), and Addendum 2 (section 5).

					Addendum 2 has not commented on the cost-effectiveness of TAVI devices for different surgical risk groups; therefore, the EAG cannot comment further. No changes have been made to Addendum 2 to address this comment
11	Stakeholder 2 Edwards Lifesciences	23		The statement "For evidence of TAVI inserted into a **native aortic** valve (that is valve-in-valve)," is inaccurate. Valve in Valve (ViV) is a TAVI in a failed bioprosthesis (TAVI in SAVR) or a failed TAVI (TAVI in TAVI). A TAVI inserted into a **native aortic** valve is simply a TAVI. (Emphasis added).	Thank you for your comment. The EAG have removed the text in brackets in the Addendum 2.
12	Stakeholder 2 Edwards Lifesciences	15, 23	Table 1, 4.5.3	The LYTEN trial had a very restrictive indication with a limited sample size. The factual accuracy of relevance of this trial for this assessment is unclear, as it focuses only on patients with a failed small (≤23 mm) surgical valve undergoing ViV-TAVR.	Thank you for your comment. This is not a factual inaccuracy. This study met the Final Scope (set and published by NICE in November 2023), which included "people with a failed previous bioprosthetic valve" and did not restrict by valve (surgical or TAV) or annulus size. The study also met the EAG study inclusion criteria and prioritisation set out in Section 3.1 of the EAG Final Protocol and Section 2.2 of the Addendum 2. The EAG have noted that this evidence is relevant to a small proportion of patients and lacks generalisability to a general population. The EAG consider that this study presents evidence for the performance of two of the three manufacturers included within this LSA that are explicitly indicated in this specific

					subgroup (see Table 2 in the original EAG Report). No changes have been made to Addendum 2 to address this comment
13	Stakeholder 2 Edwards Lifesciences	20	Table 3	Some additional clinical outcomes should be added to this table. One component of the primary endpoint was statistically different between the 2 groups. Moderate/Severe Aortic Regurgitation (AR) at 1 year was higher with the MyVal group vs. the SAPIEN 3 group (3.9% vs. 1.2%, p=0.0051). Additional secondary endpoints such as new atrial fibrillation at 1-year or VARC-3 Bleeding at 30 days, not Bonferroni corrected but impacting QALYs, also differ between the 2 groups favouring the SAPIEN 3 arm.	Thank you for your comment. This is not a factual inaccuracy; data presented in Table 3 is accurate. The EAG acknowledge that the authors conducted separate analyses of each component of the composite endpoint. From this, a statistical difference in moderate/severe aortic regurgitation was observed at 1 year (1% (6/511) with Sapien 3 and 4% (20/509) with MyVal; p=0.0051), however the EAG note that this analysis was not corrected for multiple comparisons, and the study was not powered to detect a difference in this outcome. The EAG note that additional secondary exploratory (hypothesis-generating) outcomes were reported and were not subject to Bonferroni correction. The EAG did not tabulate these outcomes as it is unclear whether the statistical difference would remain with appropriate correction applied. No changes have been made to Addendum 2 to address this comment.

ANNEX 1
Summary of outcomes from the key clinical studies identified

Systematic Reviews	# Patients	Valve	Death	Stroke	Major PVL (Mod to Sev)	PPI
Lerman *IJC, 2023*	**35,248**	Evolut R/PRO vs. S3	**In-hospital or 30D: 3.4% vs. 2.4% OR: 1.31 [1.15;1.49], p<0.001** >30D: 11.7% vs. 12.9% **OR:** 1.07 [1.00;1.16], p=0.06	In-hospital or 30D: 3.9% vs. 3.6% **OR:** 1.08 [0.96;1.23], p=0.20	**In-hospital or 30D: 8.0% vs. 4.4% OR: 1.56 [1.20;2.03], p=0.001**	**In-hospital or 30D: 32.1% vs. 22.8% OR: 1.44 [1.36;1.52], p<0.001**
Siddiqui *JSCAI, 2024*	**10,174**	BEV (S3, S3U, S3UR) vs. SEV (Evolut PRO, Evolut PRO+, Evolut FX)	1Y: **OR:** 1.15 [0.89;1.48], p=0.29	**In-hospital or 30D (Stroke/TIA) OR: 0.62 [0.44;0.87], p=0.01**	**In-hospital or 30D: OR: 0.43 [0.25;0.75], p<0.01**	**In-hospital or 30D: OR: 0.55 [0.44;0.70], p<0.01**
Wang *BMC CD, 2023*	**9,641**	Evolut R/PRO vs. S3/S3U	30D: 2.5% vs. 2% **OR:** 1.24 [0.88;1.74], p=0.07 1Y: 11.8% vs. 11.2% **OR:** 1.07 [0.85;1.34], p=0.58	30D: 3.1% vs. 1.6% **OR:** 1.76 [0.91;3.37], p=0.09	30D: 5.4% vs. 3.6% **OR:** 1.50 [0.97;2.31], p=0.07	**30D: 16.9% vs. 10.1% OR: 1.57 [1.36;1.88], p<0.00001**
Yang *IJS, 2023*	**94,115**	Evolut R/PRO vs. S3	**In-hospital or 30D: OR: 1.29 [1.18;1.40]**	**In-hospital or 30D: OR: 1.68 [1.17;2.41]**	**In-hospital or 30D: OR: 1.88 [1.26;2.82]**	**In-hospital or 30D: OR: 1.57 [1.40;1.76]**
Zhang *JCI, 2022*	**37,958**	BEV (SAPIEN, SAPIEN XT, S3) vs. SEV (CoreValve, Evolut R, Acurate Neo, Portico)	**1Y: OR: 0.88 [0.78;1.00], p=0.05**	30D: **OR:** 0.89 [0.62;1.27], p=0.48	**30D: OR: 0.40 [0.29;0.55], p<0.01**	30D: **OR:** 0.74 [0.50;1.09], p=0.12
New Meta-Analysis accepted on 10 April and published on 19 Apr 2025						
Tavakoli *CC, 2025*	**4,325**	BEV (SAPIEN, SAPIEN XT S3, S3U) vs. SEV (CoreValve, Evolut R, Evolut PRO/ PRO+/ FX, ACURATE neo, Portico)	**30D: RR = 0.54 [0.35;0.81], p=0.003** 1Y: **RR** = 0.89 [0.66;1.20], p=0.43 >1Y: **RR** = 0.95 [0.79;1.25], p=0.71	30D: RR = 1.17 [0.68;2.02], p=0.57 1Y: RR = 1.25, [0.68;2.28], p=0.47 >1Y: RR = 1.09, [0.77;1.54], p=0.61	**30D: RR = 0.28, [0.17;0.49], p<0.001** 1Y: **RR** = 0.41, [0.11;1.63], p=0.20 **>1Y: RR = 0.28, [0.10;0.79], p=0.01**	**30D: RR = 0.56, [0.37;0.87], p=0.008 1Y: RR = 0.78, [0.64;0.94], p=0.01** >1Y: **RR** = 0.86, [0.55;1.36], p=0.52

Statistically significant clinical outcomes in favour of SAPIEN 3 / S3U are highlighted in bold green text
Statistically significant clinical outcomes in favour of comparator are highlighted in bold red text

RCTs	# Patients	Valve	Death	Stroke	Major PVL (Mod to Sev)	PPI
Feistritzer JACC, 2025	**447**	SEV (Evolut R) vs. BEV (S3)	5Y: 48.5% vs. 47.6% HR: 0.98 [0.74;1.29], p=0.86	**5Y: 2.2% vs. 9.6% HR: 4.84 [1.65;14.18], p=0.002**	5Y: 9.0% vs. 5.8% HR: 0.64 [0.30;1.37], p=0.25	5Y: 29.4% vs. 22.8% HR: 0.75 [0.52;1.08], p=0.12
Nuche JACCCI, 2023	**102**	ViV BEV (S3/S3U) vs. SEV (Evolut R/PRO/PRO+)	1Y: 6.5% vs. 3.8% HR: 1.84 [0.31;11.1], p=0.495	1Y: 0% vs. 1.9%, p=0.369	Not reported	1Y: 2.2% vs. 1.9%, p=0.898
Terkelsen Lancet, 2025	**1,031**	Myval or Myval Octacor vs. S3/S3U	1Y: 5% vs. 6% ARD: -1.0% [-3.1;1.1], p=0.52	1Y: 5% vs. 5% ARD: -0.4% [-3.0;2.2], p=0.76	**1Y: 4% vs. 1% ARD: +2.8% [0.8;4.7], p=0.0051**	**1Y: 21% vs. 12% ARD: +8.9% [4.3;13.4], p=0.0002**
Retrospective Data						
Kim *JACC, 2025*	**2,106**	SEV (ACURATE Neo2) vs. BEV (S3U)	1Y: 8.5% vs. 8.4%, p=0.924	1Y: 4.6% vs. 4.4%, p=0.897	**1Y: 2.0% vs. 0.7%, p=0.033**	1Y: 8.1% vs. 9.4%, p=0.396
Loewenstein *CRM, 2024*	**3,208**	ACURATE Neo2 vs. S3	30D: 4.8% vs. 3.6%, p=0.58	Not reported	30D: 0% vs. 1.0% p = 0.35	30D: 8.9% vs. 12.2%, p=0.33
ACURATE Neo 2 IDE trial (FDA requirements) published in the Lancet on 21 May 2025 – that led to the discontinuation of the TAVI platform						
Makkar *The Lancet, 2025*	**1,500**	Acurate Neo2 vs. S3 /S3U / Evolut R / Evolut PRO / Evolut PRO+/Evolut FX	1Y: 5% vs. 3.9% HR: 1.30 [0.80;2.14], p=0.29 SAPIEN 3 : 4.1% Evolut : 3.4%	**1Y: 5% vs. 3.4% HR: 1.68 [1.02;2.75], p=0.04** SAPIEN 3 : 2.3% Evolut : 5.8%	**1Y: 3.7% vs. 1.8%, p=0.007** SAPIEN 3 : 0.2% Evolut : 4.6%	1Y: 11.2% vs. 12% HR: 0.93 [0.69;1.26], p=0.66 SAPIEN 3 : 10.9% Evolut : 14.1%

2025 surveillance report on transcatheter aortic valve implantation (TAVI) to treat aortic stenosis (NICE guideline NG208 Heart Valve Disease)

Topic areas

- Aortic valve disease - transcatheter aortic valve implantation (TAVI) to treat aortic stenosis

Context

In 2021 NICE recommended TAVI for adults with non-bicuspid severe aortic stenosis who are high surgical risk or if surgery is unsuitable. TAVI was not recommended for people at low or intermediate surgical risk. These recommendations were informed by an evidence review comparing the effectiveness of TAVI, surgery and conservative management in people with heart valve disease and an accompanying economic model. The results of the economic model showed that TAVI, at the price at time of guideline publication, was cost effective for people at high risk of surgery but not for people at low or intermediate risk. A threshold analysis was conducted to determine the price at which a TAVI valve would be cost effective, based on a willingness to pay threshold of £20,000. This threshold was found to be £15,500 for people with intermediate surgical risk and £14,800 for people with low surgical risk.

Triggers for the surveillance review

The surveillance review was triggered by information received from Edwards Lifesciences (a manufacturer of transcatheter heart values) as part of the consultation and resolution process for a draft NICE late-stage assessment which compared different types of transcatheter valves. Edwards Lifesciences argued that the approach to economic modelling in NG208 is outdated. This surveillance review considers the new information provided by Edwards Lifesciences and the potential impact on NG208 guideline recommendations.

Points raised that relate specifically to the draft late-stage assessment are not considered as part of the surveillance review.

Methods

The surveillance process consisted of:

- Literature searches to identify relevant evidence.
- Considering the new evidence and intelligence that triggered the exceptional review.
- Considering the economic aspects of the changes in the clinical evidence base.
- Considering the evidence used to develop the 2021 guideline.
- Assessing the impact of new evidence and intelligence on the current recommendations

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Search and selection strategy

We searched for reports of randomised controlled trials comparing TAVI with surgical valve replacement that have been published since the systematic search that was done as part of guideline development. Trials were included in the review if they met the criteria in Table 1.

Table 1: Selection criteria for studies included in the surveillance review

Population	People with aortic stenosis
Intervention	Transcatheter aortic valve replacement
Comparison	Surgical aortic valve replacement

Outcome	Outcomes which were relative effect parameters NG208 economic model
Study type	Randomised controlled trials
Other selection criteria	The following were not included: - Studies that only included participants with high surgical risk (TAVI is already recommended for this population in NICE guidance) - Studies that only reported sub-analysis for subgroups not included in the NG208 economic model. - Reports of trials that were excluded from the relative effect estimates for the base case analysis for NG208 (e.g. SURTAVI, NOTION)

Relevant NICE guidelines

TAVI for aortic stenosis was considered as part of NICE guideline 208 (Heart valve disease). This guideline was published in 2021 and has not yet been updated.

NICE also has interventional procedure guideline on transcatheter aortic valve implantation for aortic stenosis which assessed the efficacy and safety of the procedure and concluded that there was sufficient evidence on efficacy and safety to support the use of the procedure with standard arrangements for governance, consent and audit.

A late-stage assessment is in development to assess the incremental clinical, economic and non-clinical benefits of TAVI devices for people with severe aortic stenosis.

Other relevant guidance

Guidance for healthcare systems outside of the UK has limited applicability because the criteria for recommending TAVI were derived from a cost-effectiveness analysis that used NHS costs and was structured to reflect the way that healthcare is delivered in the UK.

The Scottish Health Technologies group produced guidance on TAVI for the treatment of people with symptomatic severe aortic stenosis who are at low surgical risk and recommend that TAVI should be considered as an option for this group.

In 2023 NHS England produced a position statement stating that TAVI could be considered as an option for people at low or intermediate surgical risk under certain circumstances. They acknowledged that NICE guideline 208 did not recommend use in these groups but cited resource benefits, stating that the use of TAVI in low and intermediate risk groups could alleviate the pressures on local systems and support elective performance.

Evidence considered when developing the guideline recommendations

Guideline recommendations were based on a systematic review of randomised controlled trials and an economic model that was produced as part of guideline development. The health economic model showed that at the list prices at the time of guideline production, TAVI was only cost effective (using a cost-effectiveness threshold of £20,000 per QALY) for people with high surgical risk.

Previous surveillance reviews

There have been no previous surveillance reviews for this guideline.

Evidence and intelligence considered in this exceptional surveillance review

New published evidence on the effectiveness of TAVI compared with surgical aortic valve replacement

Eight reports were identified, reporting on 6 studies. Key characteristics of the studies are shown in Table 2. Two of these studies reported longer-term follow up data on studies that were used to estimate relative effectiveness in the NG208 health economic model (PARTNER 3 and Evolut). Four additional studies were identified (NOTION-2, DEDICATE, UK TAVI, RHEIA). All studies were randomised controlled trials.

Table 2: Characteristics of studies included in the surveillance review

Study	Sample size	Population	Follow up	Valve type
PARTNER 3	1000	Severe symptomatic aortic stenosis and low surgical risk	5 years	SAPIEN 3 (3rd generation)
Evolut	1414	Severe aortic stenosis and low surgical risk	5 years	CoreValve, Evolut R, or Evolut PRO (1st, 2nd or 3rd generation)
NOTION-2	370	Severe aortic stenosis and low surgical risk, aged <=75 years	1 year	Any valve (physician choice)
DEDICATE	1414	Severe symptomatic aortic stenosis with low or	1 year	Acurate Neo,

		intermediate surgical risk, aged >= 65 years		Acurate Neo 2, Lotus Edge, SAPIEN XT, SAPIEN 3, SAPIEN 3 Ultra, Corevalve Evolut R, Corevalve Evolut Pro, Corevalve Evolut Pro+, Portico
UK TAVI	913	Severe symptomatic aortic stenosis, with moderately increased surgical risk	1 year	SAPIEN, SAPIEN XT, SAPIEN 3, Corevalve Evolut, Corevalve Evolut R, Corevalve Evolut Pro, Lotus, Acurate, Acurate Neo, Direct

				Flow Medical, Portico
RHEIA	443	Women with severe symptomatic aortic stenosis	1 year	SAPIEN 3 (3rd generation)

The effects reported by the studies in the surveillance review are summarised in Table 3, alongside the effect estimates used in the NG208 economic model. When studies reported at more than one time point, the effect estimate from the later time point is reported.

Table 3: Effect estimates for relative effect parameters used in the NG208 economic model and reported by studies included in the surveillance review

Outcome	**Relative effect estimates - NG208 economic model** Risk ratio (RR) <1 favours TAVI	**Relative effect estimates - surveillance review** Hazard ratio (HR) <1 favours TAVI Risk difference (RD) <0 favours TAVI
Mortality	30 days: RR 0.81 (0.55 to 1.18) 1 year: RR 0.91 (0.75 to 1.15) 2 years: RR 0.97 (0.82 to 1.16)	PARTNER 3: HR 1.23 (0.79 to 1.90) Evolut: HR 0.88 (0.66 to 1.17) NOTION-2: HR 2.00 (0.40 to 10.70) DEDICATE: HR 0.43 (0.24 to 0.73) UK TAVI: HR 0.69 (0.38 to 1.26) RHEIA: RD -1% (-3.3 to 1.3)
Stroke	30 days: RR 0.83 (0.5 to 1.39)	PARTNER 3: HR 0.87 (0.51 to 1.48) Evolut: HR 1.11 (0.77 to 1.59) NOTION-2: HR 2.00 (0.50 to 7.80) DEDICATE: HR 0.61 (0.35 to 1.06) UK TAVI: HR 1.98 (0.95 to 4.11)

		RHEIA: RD 0.3% (-3 to 3.7)
Pacemaker placement	30 days: RR 1.81 (1.04 to 3.17)	PARTNER 3: HR 1.33 (0.90 to 1.96) Evolut: HR 2.70 (2.04 to 3.55) DEDICATE: HR 1.81 (1.27 to 2.61) UK TAVI: HR 2.05 (1.43 to 2.94)
Major bleeding	30 days: RR 0.24 (0.2 to 0.29)	PARTNER 3: HR 0.65 (0.45 to 0.95) DEDICATE: HR 0.24 (0.16 to 0.35) UK TAVI: HR 0.33 (0.24 to 0.45)
Vascular complications	30 days: RR 1.46 (1.11 to 1.92)	Evolut: HR 1.07 (0.64-1.82) UK TAVI: HR 4.42 (2.54 to 7.71) RHEIA: RD 2.8% (0.2 to 2.3)
Kidney injury	30 days: RR 0.37 (0.22 to 0.59)	DEDICATE: HR 0.56 (0.24 to 1.21)
Reintervention	Latest timepoint available in study: RR 1.87 (0.69 to 5.05)	PARTNER 3: HR 0.86 (0.39 to 1.92) Evolut: HR 1.30 (0.66 to 2.56) DEDICATE: HR 1.70 (0.38 to 9.78)

		UK TAVI: HR 0.80 (0.51 to 1.23)
Hospitalisation	1 year: RR 0.73 (0.46 to 1.17)	PARTNER 3: HR 0.75 (0.54 to 1.05) Evolut: HR 0.89 (0.67 to 1.19) DEDICATE: HR 0.89 (0.66 to 1.20) RHEIA: RD -6.6% (-11.9 to -1.4)

Impact of new evidence on NICE guideline 208

At the time that the NG208 economic model was developed, there was little long-term data on the effectiveness of TAVI compared with surgical aortic valve replacement. The economic model was informed by data from 3 trials: PARTNER-2, PARTNER-3 and Evolut. Long-term data was only available from the PARTNER-2 trial, which used 2nd-generation SAPIEN-2 valves that are not currently used in the NHS.

The new evidence identified as part of this surveillance review is broadly consistent with evidence used to inform the NG208 economic model. Most of the effect estimates in the studies in the surveillance review are reported as hazard ratios, whereas the effect estimates in the economic model are risk ratios, so the magnitude of the effects cannot be directly compared. However, the direction of the effects in the studies identified in the surveillance review are mostly consistent with those in the economic model for all outcomes. One possible exception is for the 'reintervention' outcome. The NG208 economic model used a meta-analysis of the PARTNER 2, PARTNER 3 and Evolut trials to estimate the relative effect of TAVI vs surgical aortic valve replacement on this outcome. The PARTNER 2 trial used a 2nd-generation valve (SAPIEN 2) which is no longer used by the NHS. The relative effect for this trial at 5 years follow up was HR=3.28 (1.32 to 8.13), which favours

surgical aortic valve replacement. The HR for all trials included in this surveillance review was lower, with no trial showing a statistically significant difference between treatments, suggesting that the NG208 economic model may overestimate the reinterventions needed for TAVI for the valves currently used in the NHS. The committee for NG208 did acknowledge that the reintervention rate might be lower with newer generation valves. To address this, a scenario analysis was conducted with the relative effect for the reintervention rate estimated from trials of 3rd generation valves only (which was close to a relative effect of 1). This did not affect the conclusions on cost effectiveness drawn from the model.

Price of TAVI valves

The average price across TAVI valves used the NG208 economic model was £17,500. As of November 2023, the evidence assessment group for the NICE late-stage assessment on TAVI devices calculated the weighted average TAVI valve cost (post Specialised Services Devices Programme [SSDP] with rebate using market share) was [redacted].

Impact of updated prices on NICE guideline 208

The price estimate for TAVI valves used by the NICE late-stage assessment is [redacted] than the price used in the NG208 economic model. However, a threshold analysis was conducted as part of the economic modelling to determine the price of TAVI that would mean that it would become cost-effective. 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. [redacted].

Information provided during the late-stage assessment resolution process

The information submitted by Edwards Lifesciences, together with responses are presented in table 4.

Table 4: Comments provided by Edwards Lifesciences during the late-stage assessment resolution process

Comment provided by Edwards Lifesciences	**Response**
Estimate for Moderate / Severe PVL for TAVI at 30 days is wrong as it is coming from an estimate at 1-year follow-up. Indeed, the 2.7% estimate for Moderate/Severe PVL used in the NICE model for TAVI corresponds to a 1-year estimate (not at 30 days) from the SOURCE 3 registry, which was published in 2017 publication by Wendler at al.[3] Moreover, this 1-year estimate was not based on a low-risk population but on a high-risk cohort with a logistic EuroScore of 14% for the TF cohort. This is important as this reflects an increased risk ratio for TAVR > 10, as the estimate considered for SAVR is 0.2%. Using the 30-days data from the PARTNER 3 trial (0.8% for SAPIEN 3 and 0% for SAVR), the impact on the results would be significant as the model is highly sensitive. The incremental QALY gain would increase to 0.04 (+69%).	A similar comment was raised by Edwards Lifesciences at the time of guideline development (see page 256 in the stakeholder comments and responses where Edwards Lifesciences comment that a different result would have been obtained if the model had been populated solely with data from the PARTNER 3 trial). This comment does not relate to information that has become available since the time of guideline publication. The NG208 economic model estimated the rate of paravalvular leak in the TAVI group from the SOURCE 3 dataset and used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative effect for TAVI versus surgical aortic valve replacement. As noted in the response to stakeholders at the time of publication, it would not be appropriate to base the analysis on a single RCT because:

	• in the NICE reference case, meta-analysis of multiple RCTs are preferable to single RCTs • PARTNER 3 is focused on a single valve (SAPIEN 3). This analysis is not assessing whether a particular valve is cost-effective in England, but whether TAVI in general is cost-effective. We are aware that different valves have different performances for examples regarding paravalvular leak. Therefore, a more comprehensive approach, using trials of different 2nd and 3rd generation valves was preferred. • The committee wanted to be able to make a differential recommendation based on surgical risk as they expected different level of cost-effectiveness in different risk groups. This would not be possible if the analysis was conducted on low-risk patients only using PARTNER 3. Using an estimate from a real-world data-source to estimate the risk in the TAVI group and data from RCTs to estimate the relative effect is preferable to an approach that uses absolute risks derived solely from

	randomised controlled trials, where the participants are unlikely to be representative. The committee did acknowledge that the reintervention rate (which is related to the paravalvular leak rate) might be lower with 3rd generation valves. To address this, a scenario analysis was conducted with the relative effect for the reintervention rate estimated from trials of 3rd generation valves only (which was close to a relative effect of 1). This did not affect the conclusions on cost effectiveness drawn from the model.
Stroke incidence for both groups TAVI and SAVR at 30 days. The 2.1% estimate for TAVI in the NICE model is coming from the 2019-2020 NICOR dataset.[4] A risk ratio of 0.83 was used (TAVI vs. SAVR), based on a review of many RCTs (including trials conducted for intermediate risk patients, 2nd generation of TAVI valves, and alternative non-transfemoral access), leading to a 2.5% stroke incidence estimate for SAVR. If we consider data from our latest PARTNER 3 trial for low-risk patients, the	A similar comment was raised by Edwards Lifesciences at the time of guideline development (see page 256 in the stakeholder comments and responses where Edwards Lifesciences comment that a different result would have been obtained if the model had been populated solely with data from the PARTNER 3 trial). This comment does not relate to information that has become available since the time of guideline publication. See the first response for details of why it would have been inappropriate to base the analysis on a single RCT.

corresponding incidence rates are slightly different with a larger difference between SAPIEN 3 and SAVR (0.6% vs. 2.5%, RR = 0.25). Using these two estimates completely changes the results of the model. The incremental QALY gains double and increases to 0.051 (+116%).	The NG208 economic model estimated the rate of stroke incidence in the TAVI group from the UK TAVI audit 2020 and used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative effect for TAVI versus surgical aortic valve replacement. A sensitivity analysis was conducted with a relative effect for all treatment effects based on a meta-analysis of all RCTs identified in the evidence review for the guideline which led to an increase in incremental costs per QALY across risk groups. We also note that the 5-year data from PARTNER 3 (which was not available at the time of guideline publication) shows a HR of 0.87 which shows a smaller benefit in terms of stroke incidence that at earlier timepoints in the trial and is similar to the relative effect used in the NICE model.
Major bleeding incidence for both groups TAVI and SAVR at 30 days. The 2.3% estimate for TAVI in the NICE model is coming from the 2019-2020 NICOR dataset. A risk ratio reduction of 0.24 has been estimated based on a review of	A similar comment was raised by Edwards Lifesciences at the time of guideline development (see page 256 in the stakeholder comments and responses where Edwards Lifesciences comment that a different result would have been obtained if the model had been populated solely with

many RCTs (including trials conducted for intermediate risk patients, 2nd generation of TAVI valves, and alternative non-transfemoral access), leading to an estimate for SAVR of 9.4%. If we consider data from our latest PARTNER 3 trial for low-risk patients, the corresponding incidence rates are slightly different with a larger difference between SAPIEN 3 and SAVR (1.2% vs. 11.9%, RR = 0.1). Using these 2 estimates slightly changes the results of the model, as the incremental QALY would increase to 0.03 (+27%).	data from the PARTNER 3 trial). This comment does not relate to information that has become available since the time of guideline publication. See the first response for details of why it would have been inappropriate to base the analysis on a single RCT. The NG208 economic model estimated the rate of major bleeding in the TAVI group from the UK TAVI audit 2020 and used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative effect for TAVI versus surgical aortic valve replacement. A sensitivity analysis was conducted with a relative treatment effects based on a meta-analysis of all RCTs identified in the evidence review for the guideline which led to an increase in incremental costs per QALY across risk groups.
Permanent pacemaker incidence for both groups TAVI and SAVR at 30-days. The 9.7% estimate for TAVI in the NICE model is coming from the 2019-2020 NICOR dataset considering both balloon-expandable and self-expandable valves. An increased risk ratio of 1.81 (vs. SAVR) has been	A similar comment was raised by Edwards Lifesciences at the time of guideline development (see page 256 in the stakeholder comments and responses where Edwards Lifesciences comment that a different result would have been obtained if the model had been populated solely with data from the PARTNER 3 trial). This comment does not relate to

estimated based on a review of many RCTs (including trials conducted for both balloon-expandable and self-expandable valves), leading to an estimate for SAVR of 5.4%. The large difference in permanent pacemaker between the 2 types of valves is well-known and is also reflected in the 2019-2020 NICOR dataset (slides #60-61), with a 7% incidence for the balloon-expandable SAPIEN 3 valve vs. 14.8% for the self-expandable valve. The 7% incidence with SAPIEN 3 is actually very close from the TAVI with SAPIEN 3 arm of the PARTNER 3 trial (6.6%). The difference between SAPIEN 3 and SAVR became much smaller with 6.6% and 4.1% for SAPIEN 3 and SAVR respectively (RR = 1.65). Plugging the PARTNER 3 results with these two estimates slightly changes the results of the model; the incremental QALY increases to 0.03 (+27%)	information that has become available since the time of guideline publication. See the first response for details of why it would have been inappropriate to base the analysis on a single RCT. The NG208 economic model estimated the rate of permanent pacemaker incidence in the TAVI group from the UK TAVI audit 2020 and used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative effect for TAVI versus surgical aortic valve replacement. A sensitivity analysis was conducted with a relative treatment effects based on a meta-analysis of all RCTs identified in the evidence review for the guideline which led to an increase in incremental costs per QALY across risk groups.
Mortality estimates at 30 days for both groups TAVI and SAVR. The 30-days mortality considered for SAVR is 0.7% and is coming from the National Adult Cardiac Surgery Audit (NACSA) report,[5] but we were not able to find this	The NG208 economic model estimated the rate of mortality at 30 days for the surgical aortic valve replacement group from the National Adult Cardiac Surgery Audit 2020 and used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative

figure in the report referred in the economic report of the NICE guideline (NG208). A reduced risk (RR = 0.81) is applied for the 30-days mortality for TAVI – estimated from a review of many RCTs (including trials conducted for intermediate risk patients, 2nd generation of TAVI valves, and alternative non-transfemoral access) leading to a 30-days mortality of 0.6% for TAVI. If the 0.6% 30-days mortality for TAVI is not too far from the one in PARTNER 3 (0.4%), we are surprised about the 0.7% for SAVR – which strongly outperforms the 1.1% from the surgical arm in PARTNER 3 and its legitimacy could be questioned. When looking into more details from the NACSA report, we find crude mortality rate for all cardiac procedures with a 2.44% estimate but no stratification for isolated SAVR and by risk scores. A quick review of “contemporary” real-world evidence comparing 30-days mortality between TAVI and SAVR for low-risk patients have been produced (see Appendix 2). The mortality at 30 days in the NICE model appears low compared with the literature (ranges from 1.1% to 3.6%), so the 0.7% from NICE does appear to be	effect for TAVI versus surgical aortic valve replacement. A sensitivity analysis was conducted with a relative treatment effects based on a meta-analysis of all RCTs identified in the evidence review for the guideline which led to an increase in incremental costs per QALY across risk groups.

underestimated. If we consider data from our latest PARTNER 3 trial for low-risk patients, the difference in 30-days mortality between SAPIEN 3 and SAVR (0.4% vs. 1.1%, RR = 0.37) increases. Using these 2 estimates changes slightly the results, and the incremental QALY increases to 0.027 (+14%).	
It seems there are inconsistencies in the formulae used between the low-risk and the high-risk model in the extrapolation of monthly utilities between data points during the first year – and we believe the approach and linear formulas used for the high-risk model are accurate (see sheet 'D5 utility' in the NICE model). For example, the utility extrapolation for the 2nd Month (UtilityM2) should be calculated and linearly extrapolated using the following formula: $(Utility_{M6} – Utility_{M1})/5 + Utility_{M1}$ instead of $(Utility_{M6} – Utility_{M1})/4 + Utility_{M1}$	As highlighted in this comment, there was an error in the formula to extrapolate quality of life in people with intermediate and low risk. After correcting for this, the incremental QALYs in the low risk population increased by 0.002 (equal to a % increase as stated in the comment). The overall effect is relatively small and did not affect the recommendation for people with low or intermediate risk. Similarly, the effect on the TAVI price threshold analysis was limited, resulting in only a £100 increase in the cost-effectiveness threshold for the valve in both low- and intermediate-risk groups.

This issue in the formula occurs also for the subsequent utilities until the 5th Month. The same issues occurred for the extrapolation between the 7th month and the 11th month. For example, the utility extrapolation for the 7th Month (UtilityM7) should be calculated and linearly extrapolated using the following formula: $(Utility_{Y1(M12)} – Utility_{M6})/6 + UtilityM6$ instead of $(Utility_{Y1(M12)} – Utility_{M6})/4 + Utility_{M6}$ This is likely to be a typo or mistake in the formula, which has an impact as it reduces the 1-year utility gains for TAVI from 0.0135 to 0.0162 when corrected (a 20% increase). The model is highly sensitive, as a tiny correction in the utility extrapolation formula in the low-risk model (using the same formula used for the high-risk population) impacts the incremental QALY to 0.026 (+10%).	
Long-term mortality assumptions.	The NG208 NICE model uses mortality data from the UK national TAVI registry, collected between 2007 and 2014 to calibrate the model for long term mortality in the stable health state. However, it was noted that

This critical component is one of the most impactful in the results of the NICE model. The rationale behind its construction is quite complex and somehow unexpected – knowing the large amount of contemporary evidence existing in the literature nowadays. The long-term mortality calculation for the "Stable" health state is constructed combining 3 assumptions: ▪ A significant reduction of the TAVI relative survival versus the general population – specific to intermediate risk (IR) as a reference – based on a study from the UK including 6,420 patients treated with TAVI from 2007 to 2014. The relative survival reduction with TAVI for IR in comparison to the general population are 91.7%, 89% and 85.5% at 1-year, 2-years, and 3-years respectively. ▪ A specific hazard ratio of increased morality for HR (2.7) and IR (1.6) vs. LR – based on a study from Israel which includes 1,327 patients treated with	during this period, valves used in the NHS were most likely 1st and 2nd generation valves, so it is possible that survival benefits have increased in recent years following the introduction of new generation valves. Therefore, a sensitivity analysis was conducted where the survival of people at low surgical risk was assumed to be equal to the survival of the general population in the UK estimated though the life tables for England 2018-2019. The sensitivity analysis did not change the conclusions of the analysis. The NG208 economic model used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative effect for TAVI versus surgical aortic valve replacement on mortality at 1 and 2 years. See the first response for details of why it would have been inappropriate to base the analysis on a single RCT. The data from PARTNER 3 at 5 years was not available at the time of guideline publication. However, we note that the latest 5 year data from the PARTNER 3 trial reported a higher mortality in the TAVI group than the surgical aortic valve replacement group, contrary to the data at 1 and 2 years (HR=1.23 (95% CI 0.79 to 1.0)).

TAVI from 2008 to 2014. So, in order to convert IR to LR, a calculated hazard ratio (1/1.6) is applied. ▪ A third hazard ratio reducing the TAVI mortality (vs. SAVR) calculated from a clinical review from combined RCTs, including trials conducted for intermediate risk patients with 2nd generation of valve, including alternative access and combining both balloon and self-expandable TAVI valves. The corresponding HR are 0.93 and 0.97 at 1-year and 2-years respectively. Then, for the other health states, specific increased hazard ratios are added on top to account for the excess risk of mortality – which is common practice in health economics modelling. However, due to the use of the previous data a 'calibration factor' was used so the mortality in year 3 in the model matches the mortality outcomes of the studies described above.	

Construction of the long-term survival estimates from a combination of 3 various components – including some complex calibration which is difficult to fully understand. One example is that it seems impossible to set exactly equal mortality for TAVI and SAVR – as the whole simulated cohort is being multiplied by the 30-days mortality rate with TAVI (0.7%) and the converted patients to SAVR (0.55%) are also multiplied by this death rate – suggesting that the deaths and other events for these converted to SAVR patients are being double counted. Also, despite a favorable hazard ratio reducing TAVI mortality, the total life-year gains favor SAVR (10.61 for TAVI vs. 10.67 for SAVR), which is counter-intuitive based on the evidence used and is not confirmed by any longer-term evidence. The data used from both studies are outdated and do not represent what is expected in clinical practice today in the low-risk population. Patients treated in 2007-2014 did not benefit from our latest TAVI technologies (SAPIEN 3 was	

introduced in late 2014) and the non-transfemoral approaches represented proportionally a significant number of cases (24% from the 2012 BCIS audit vs. ~5% in the latest one from 2019/2020) – as the catheter diameters were larger. Below a summary table is presented with the various mortality rates considered from NICE, the general population and from our PARTNER 3 trial at 1 and 2-years for the low-risk patients – for both TAVI and SAVR respectively.

Mortality Rates	**From NICE**	**From Gen. Pop.**	**From PARTNER 3**
@ 1-year	7.3% / 7.9%	3.5%	1.0% / 2.5%
@ 2-year	10.7% / 11.0%	6.2%	2.5% / 3.2%

As we can see from the table above, the PARTNER 3 data is outperforming the mortality rate from the general population; thus, life tables from the general population may be more realistic and should be considered, but without any additional excess risk of mortality after TAVI (as seen in economic models described in the literature summarized in the table below).

The all-cause mortality treatment effects considered by NICE are based on combining various RCTs (including trials for intermediate risk patients, 2nd generation of TAVI valves, balloon and self-expandable TAVI valves, and alternative non-transfemoral access) and do not reflect the hazard ratio from the PARTNER 3 trial or the ones calculated from specific low-risk meta-analyses.

Hazard Ratio (HR) –	**From NICE**	**From PARTNER 3**

All cause mortality			
@ 1-year	0.93	0.41	
@ 2-year	0.97	0.75	
Aortic valve re-intervention. The assumption of an increased risk for TAVI, with a calculated HR = 1.87, is based on a compilation of many RCTs, including trials with intermediate risk patients (2nd generation of TAVI valves removed from the UK market in 2014), balloon and self-expandable TAVI valves, and alternative non-transfemoral access. The latest 5-year available data with SAPIEN 3 from the PARTNER 2 S3i cohort, assessing and comparing the 5-year incidence of structural valve deterioration (SVD) using the latest VARC 3 criteria between SAPIEN XT, SAPIEN 3TM and SAVR was not considered. In this trial, the various rates of SVD (SVD-related bioprosthesis valve failure (BVF), and all-cause BVF) with SAPIEN 3 were not different to SAVR and were significantly lower versus			The committee did acknowledge that the reintervention rate (which is related to the paravalvular leak rate) might be lower with 3rd generation valves. To address this, a scenario analysis was conducted with the relative effect for the reintervention rate estimated from trials of 3rd generation valves only (which was close to a relative effect of 1). This did not affect the conclusions on cost effectiveness drawn from the model. The latest 5-year data from the PARTNER 3 trial was not available at the time of guideline publication, but it is consistent with the earlier data from that trial. See response to the first comment for details on why it would be inappropriate to base the analysis on a single RCT.

SAPIEN XT. This was also confirmed in the recent 5-year follow-up of the PARTNER 3 trial (specifically for low-risk patients). Considering the latest data with SAPIEN 3 and a corresponding HR = 1 (no difference), the impact on the results is large, as the incremental cost is reduced by 44% to £1,849 and the incremental QALY increases to 0.038 (+61%).	
Similar situation for re-hospitalization, with a reduced HR for the 1st year (HR=0.73), and beyond, the opposite with an increased HR = 1.91 used in the NICE model – based on the same RCTs compilation. From the PARTNER 3 trial, the 1-year and 2-years re-hospitalization hazard ratios are much lower with HR = 0.63 and HR = 0.67 respectively. From the latest 5-years data from the PARTNER 3 trial, the overall HR for re-hospitalization is 0.75 – quite far from the 1.91 used in the NICE model.	The NG208 economic model used 3 trials of 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to estimate the relative effect for TAVI versus surgical aortic valve replacement. A sensitivity analysis was conducted with a relative-risks for all treatment effects based on a meta-analysis of all RCTs identified in the evidence review for the guideline which led to an increase in incremental costs per QALY across risk groups. The latest 5-year data from the PARTNER 3 trial was not available at the time of guideline publication, but it is consistent with the earlier data from that trial. See response to the first comment for details on why it would be inappropriate to base the analysis on a single RCT.

Since the publication of NG208, there have been many high-quality cost-effectiveness publications which show comparisons of the valves involved in the LSA (see full list on page 11). One of these is a UK based study of Evolut four-year data, with TAVI improving survival by 0.41 life years and added 0.28 QALYs at incremental cost of £5,021, resulting in a lifetime ICER of £17,883 per QALY gained2; another has just been submitted based on the five-year data from the PARTNER 3 trial with similar results (+0.46 QALYs gained with an increased cost of £7,998 per patient over a lifetime horizon, leading to an incremental cost-effectiveness ratio of £17,349 per QALY). :	The most relevant study published after the guideline is a cost-utility analysis based on the Evolut low-risk trial, which assessed the cost-effectiveness of Evolut R or Evolut pro compared to SAVR. The analysis is applicable to the UK NHS perspective, as the authors used different sources relevant to this setting, such as the NHS Collection Cost and the UK TAVI trial. The analysis differed from the TAVI model in NG208 for the following main reasons: 1. It focuses on only one platform of TAVI (Evolut) whereas the NG208 used a meta-analysis of trials on different valves 2. It uses data from Evolut up to 4 years whereas, at the time of NG208 publication, data up to 2 years only was available 3. It estimated a cost of SAVR much higher than the one used in NG208 Point 1 and 2 lead to a significantly higher treatment effect. In particular, based on the Evolut data, the authors made a long-term survival extrapolation projecting a significant mortality benefit of TAVI up to 15

	years since the intervention. This does not align with evidence from other trials on 3rd generation valves, such as PARTNER 3, where the improvement in survival disappeared at year 3. The authors estimated a cost of SAVR equal to £21,197, which is much higher than the cost of £13,898 used in NG208 model. This is because the authors included the cost of complex surgeries, using proportions reported in the Evolut trial, and used ICU and HDU usage data coming from the recently published UK TAVI trial. At the time of NG208 publication, UK TAVI trial results were only partially available, so the TAVI model included only median ICU days (which were lower than the mean) and no HDU. Using the mean values for ICU and HDU reported in Blackman et al (2024) significantly reduces the difference in cost between a TAVI and SAVR procedure. Keeping all other assumptions the same, and using the data from Blackman (2024), TAVI becomes cost effective (using a willingness to pay threshold of £20,000/QALY) for the intermediate risk group but not the low-risk group (cost per QALY = £33,470).

Impact of information provided during the late-stage assessment resolution process on NICE guideline 208

Most of the information provided during the late-stage assessment process is unlikely to impact on the recommendations in NG208 for the reasons outlined in Table 4. However, the publication of estimates of ICU and HDU usage data in the UK TAVI trial may have an impact on guideline recommendations because the cost estimates used in the NG208 economic model, particularly in the surgical aortic value replacement group, were lower than those reported in the UK TAVI trial, and preliminary analysis suggests that this may mean that TAVI becomes cost effective for people with intermediate surgical risk.

Impact of evidence and intelligence considered in this surveillance review on NICE guidelines

Budget impact/Economic considerations

NG208 economic model estimated the mean total cost per patient was £30,234 for TAVI compared with £27,973 for surgical aortic valve replacement for people at intermediate surgical risk and £33,333 for TAVI compared with £30,915 for surgical aortic valve replacement for people at low surgical risk. Recommending TAVI for a broader population would therefore be more costly.

System impact

TAVI is already delivered by the NHS as an intervention for aortic valve stenosis for people at high surgical risk and for people for who surgery is not suitable. Therefore, existing infrastructure and expertise is already available, although recommending TAVI for a broader population could put pressure on existing services.

Population impact

A UK population-based modelling study estimated that severe aortic stenosis affects 1.48% of people in the UK who are aged 55 or older, with 6.2% at high surgical risk, 13.9% at intermediate surgical risk and 79.9% at low surgical risk.

Symptoms include fainting, exercised-induced chest pain, breathlessness and congestive heart failure. Without treatment, prognosis is poor, with average survival following diagnosis of 2-3 years.

Health inequalities

Analysis of a large UK data set showed health inequalities in access to heart valve replacement procedures, with women less likely to undergo aortic valve

replacement than men, and people of Black and South Asian ethnicity less likely to undergo aortic valve replacement that people of White ethnicity.

There is evidence of geographic variation in the availability of TAVI, which may lead to inequalities in service provision which might be exacerbated if TAVI is recommended to a wider group of people.

How this fits with NICE priorities

This topic does not fall under topics identified as a priority in the NICE forward view.

Summary of new evidence and intelligence

This surveillance review has identified new information that has become available since the NICE guideline on heart valve disease was developed that has potential impact on recommendations on TAVI for severe aortic stenosis.

Specifically:

- Long term follow-up data are now available on the effectiveness of TAVI compared to surgical aortic valve replacement for valve types that are currently used in the NHS. The NG208 economic model relied partly on data from a study that used a valve that is no longer in use in the NHS. There is some evidence that the reintervention rate may be lower with newer generation valves, which could have an impact on the cost effectiveness of TAVI.

- The price of TAVI valves is now estimated to be [redacted] than the price used in the NG208 economic model.

- Data on resource use is now available from the UK TAVI trial which suggest that resource use, particularly in the surgical aortic valve replacement group, was underestimated in the NG208 economic model. Preliminary analysis suggests that, keeping other parameters constant, this change makes TAVI more cost effective, with the ICER for the

intermediate risk group falling below the willingness to pay threshold of £20,000/QALY.

Taken together, these factors mean that if a new economic model was developed with the most recent data, the cost effectiveness may change. Additionally, the threshold price at which TAVI will be cost effective that was calculated using the NG208 economic model is highly likely to be affected if the most recent data were to be incorporated into a new model.