Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Abbott Medical UK	Economic report MitraClip	012	016	We disagree with the cost of the procedure used. The commissioning policy states that the procedure is described by OPCS code K358 which in turn maps to HRG EY22. The tariff and reference costs attached to this HRG are much less than used in the economic model hence much less is paid for the procedure by the NHS than has been used in the model. The economic analysis should be repeated using the procedural price actually paid by the NHS.	Thank you for your comment. Costs estimated through a bottom-up approach are usually preferred in health economics analysis as they more closely reflect the real price for the NHS of a particular procedure. The cost used in the model was calculated in the Commission through Evaluation report using costs coming directly from UK sources and the manufactures, so it is considered highly reliable. Moreover, it is relatively comparable to the cost assumed in other health economics analysis conducted in the UK (Shore 2020). The tariff attached to HRG EY22 is much cheaper because it does not include the cost of the device as MitraClip is included in the High-Cost Tariff-Excluded Devices and therefore not reported in the NHS Reference Cost. If we add the cost of MitraClip from the supply chain (minus VAT) we

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					obtain a procedure cost not dissimilar to the lower case cost estimation used in the model.
Abbott Medical UK	Guideline	005	004	Assessment within 4 weeks may not be defined as urgent. A better form would be 'Offer urgent specialist assessment within 2 weeks…. Urgency is important because when valve disease becomes symptomatic, survival can decline rapidly.	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks
Abbott Medical UK	Guideline	005	017	We suggest 'Advise adults with mild valve disease that this often does not cause symptoms….'	Thank you for your comment. The committee has edited the recommendation and now use the term 'be aware' as it is aimed at health professionals and people affected by the condition
Abbott Medical UK	Guideline	010	003	Surgery may not be deemed to be appropriate by the multi-disciplinary team. It would be best to say 'surgery or percutaneous intervention'.	Thank you for your comment. We have edited the rec and now say 'intervention' as we recommend both surgery and TAVI depending on whether the former is suitable or not.
Abbott Medical UK	Guideline	011	012	We suggest adding 'repeated same interventions'.	Thank you for your comment. Repeated same interventions would be included under 'other cardiac procedures'
Abbott Medical UK	Guideline	012	006	We suggest changing to 'Offer TAVI, if suitable, to adults with non-bicuspid severe aortic stenosis, if surgery is unsuitable, following published 2020 AHA and ACC guidelines'.	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation.
Abbott Medical UK	Guideline	013	011	We suggest 'Consider transcatheter edge-to-edge repair or transcatheter mitral replacement…'	Thank you for your comment. No clinical evidence was identified for this question. An economic model suggested the intervention was cost effective but as the study had limitations a consider recommendation was made. The committee noted that the lack of evidence may be because it is well established that medical management does not improve outcomes and transcatheter mitral valve repair is useful when surgery cannot be performed. For this reason the committee did not make a research recommendation.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Abbott Medical UK	Guideline	014	003	We suggest 'Offer medical management **before** transcatheter mitral repair or replacement.' That way, transcatheter therapies remain options that clinicians can offer if medical management has failed.	Thank you for your comment. The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management. The current recommendation does not preclude mitral edge-to-edge repair being undertaken if medical management fails to control symptoms. We have added a recommendation to make this clearer (1.5.14).
Abbott Medical UK	Guideline	014	003	We suggest adding 'Patients should be referred back to the multi-disciplinary team if mitral regurgitation symptoms persist after medical management has been optimised.'	Thank you for your comment. We have added a recommendation to make it clearer that transcatheter edge to edge repair can be considered if symptoms persist

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					despite medical management. The person may be referred back to the multi-disciplinary team to discuss this as you suggest.
Abbott Medical UK	Guideline	017	014	We suggest including fitness for general anaesthesia and transoesophageal echocardiography as criteria for suitability for TAVI.	Thank you for your comment. The committee agree that fitness for the procedures is important but they wanted to highlight issues specific to TAVI rather than more general considerations that are relevant for a range of procedures.
Abbott Medical UK	Guideline	042	009	It would be best not to pool studies if the populations are different.	Thank you for your comment. There was not considered to be sufficient reason not to pool the REDUCE FMR study with COAPT and MITRA-FR studies, as the review protocol (see Appendix A) did not specify that comparisons should be stratified by operative risk or suitability for surgery. In addition, there is very little overlap between REDUCE FMR and the other two studies in terms of outcomes that are reported or the way they have been reported, meaning there are very few outcomes where data from all three studies have been

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					pooled. Where they were pooled and heterogeneity observed, with results in the REDUCE FMR trial suggesting opposing results to the other two studies, results are presented separately for REDUCE FMR.
Abbott Medical UK	Guideline	042	014	We dispute that MitraClip has been demonstrated in a study to do harm, so we request that 'some a harm' be removed from the guideline and there is no reference to harm put anywhere in the guideline.	Thank you for your comment. 'Harm' is a standard term used in NICE guidelines to describe increased negative outcomes or reduced positive outcomes in an intervention group compared to the comparator. We have clarified that this term is used to mean a 'lack of benefit'. In line with other NICE guidelines, the committee considered the clinical importance of outcomes based on the absolute risk difference. This is described in the methods chapter, section 2.7.
Abbott Medical UK	Guideline	General	General	The guideline should reflect aspirations for the future ie. what should be.	Thank you for your comment. Recommendations have been made based on current evidence to support how heart valve disease is diagnosed and managed in the future. Emerging evidence will be identified through the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					surveillance programme at NICE and this will inform any future updates.
Abbott Medical UK	Guideline	General	General	There is no mention of multi-disciplinary team deciding the best option for the patient. It would be good to include a statement to this effect.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
All Party Parliamentary Group on Heart Valve Disease	Comments form	Q3		**3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)** o To ensure that the general public are aware of the heart valve disease 'red flags', such as breathlessness, dizziness or light-headedness when carrying out everyday tasks, as well as the prevalence of the condition, it would be beneficial to establish a national awareness campaign. Awareness of the signs and symptoms is crucial to early detection and saving lives. As part of this campaign, nationwide testing could be undertaken for over-65s to receive regular stethoscope checks to help identify heart murmurs in this at-risk demographic. Within the UK the rates of auscultation in primary care are significantly lower than in some European counties. A national detection programme would therefore help to address this by ensuring heart murmurs are detected earlier, which in	Thank you for your comment. This guideline should raise the profile of heart valve disease and support health professionals to make an early diagnosis through the identification of signs and symptoms that should trigger a referral. Any future update of this guideline could include to a reference national screening programme should one be in place. Your comments will be considered by NICE where relevant support activity is being planned.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				turn means referrals for echocardiography and treatment, if needed, would also occur more speedily than is currently the case. Early detection enables swifter treatment, provides peace of mind for patients and is more economical as treating the disease earlier rather than later is far more cost effective for the NHS. The adoption of a national screening programme, could coincide with the annual flu vaccination or the potentially annual COVID-19 vaccination programmes, which would minimise cost and ensure large numbers of age appropriate people were included. o To ensure that the reach of the campaign is maximised, the use of innovative technology could be adopted, such as specialist apps, patient videos or social media graphics as well as partnerships with key organisations such as the British Heart Foundation, Heart Valve Voice and Silversurfers to help extend the campaigns reach. o Finally, community champions could be enlisted and trained to help with the roll out of the message. Once established the community champions would be an excellent way of continuing contact with, particularly hard to reach groups, which is particularly beneficial for those who do not speak English as a first language.	
All Party Parliamentary Group on Heart Valve Disease	Comments form	Q4		**4. The recommendations in this guideline were largely developed before the coronavirus pandemic. Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.** o COVID-19 has placed an extraordinary strain on NHS and because of this pressure, thousands of patients have experienced delays to treatments, with many patients also refraining from going to see their GP. According to Hospital Episode Data, Aortic valve replacements (AVR), the most common form of valve disease treatment, fell by 29% vs LY (April -	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				September 2020). This equates to 1,635 lost treatments, creating an increasing backlog of patients in the system requiring treatment. To ensure that patients receive timely treatment, GPs should continue to refer patients with symptoms of heart valve disease to secondary care and treatment options should be reassessed so that Multidisciplinary Heart Teams can determine whether a less-invasive procedure, which can significantly decrease the number of days patients need to remain in a hospital, is appropriate under the current circumstances. o The COVID-19 pandemic has demonstrated that rapid innovation can be introduced into the healthcare system and that it can be used to drive momentum for improvements in the heart valve disease patient pathway. An example of innovation shared with the APPG are several options to leverage assisted diagnosis utilising artificial intelligence and screening algorithms offered by the use of digital stethoscopes. The use of digital stethoscopes can further add value to the screening pathway as they can be performed by trained but not necessarily medically-qualified personnel e.g. a digital e-stethoscope can be used by a pharmacist or a nurse to effectively triage patients via a simple yes/no to the presence of a murmur. Overall, the barrier to adoption of new innovative techniques for the diagnosis and treatment of adults with heart valve disease will largely be cost driven, although this should be assessed in the context of the additional benefits that such technologies can bring. For example, greater accuracy in primary care can lead to more, correctly triaged and possibly diagnosed patients being referred for diagnosis and treatment downstream, potentially avoiding emergency presentations. o The APPG also supports NHS England's move to introduce 'one stop shops' for diagnostics in the community as part of the NHS Long Term	interventions are clinically and cost effective. Implementation of these should take the current context into account. We will pass your comment on digital stethoscopes onto the surveillance team at NICE for when this guideline is considered for update. Your comments on 'one stop shops' will be considered by NICE where relevant support activity is being planned.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Plan. These hubs provide an ideal location to undertake transthoracic echocardiograms, as well as other diagnostic procedures. The portability of echo machines has already resulted in many community echo clinics across the UK being established and the drive to provide off-site cardiac physiology investigations during the pandemic has accelerated this process, allowing patients to attend a community centre for a full echo study, just as they would have in hospital departments. However the expansion on these hubs should continue so that patients can receive timely diagnosis, diagnosis backlogs caused by the pandemic can be reduced, and to ensure that much needed hospital capacity is freed-up. o The pandemic has also highlighted inequalities in access to treatment across the country, which has been caused by a mixture of capacity and commissioning issues across the patient pathway. One example given to the APPG was access to Transcatheter Aortic Valve Implantation (TAVI) in the UK which is limited with large-scale geographical inequity. It was highlighted to the APPG using data from the National Institute for Cardiovascular Outcomes Research (NICOR) that there was an 11-fold variation in TAVI numbers per million population (pmp). Access to transcatheter aortic valve replacement (TAVR) was even more profound, with access concentrated around the seven centres offering this treatment, with no procedures at all performed in patients from 94 CCGs in England. For example, a patient is more likely to receive rapid treatment in the South of England than the Midlands and North, with Wales only having two Heart Centres. There is also inequity on an international scale, with far fewer TAVI procedures performed in the UK than other Western European countries, with 78 TAVIs per million population, compared to a European average of 141 (Ali et al., OpenHeart 2021). Following the COVID-19	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				pandemic, addressing inequity of access to treatment should be considered a priority by the NHS to ensure that patients can receive the right care for them and that they can return to a good quality of life.	
All Party Parliamentary Group on Heart Valve Disease	Guideline	005	004-006	The APPG for HVD supports the guideline's decision to offer urgent (ideally within 4 weeks) specialist assessment or an urgent echocardiogram to adults with a systolic murmur and exertional syncope. This was raised by healthcare professionals the APPG heard from during its evidence session. However, since the pandemic, waiting lists for heart valve disease patients have grown substantially. To ensure that this 4 week target is met, it was discussed that enhancing the provision of education programmes for healthcare professionals could enable GPs to operate community echocardiography services in line with British Society of Echocardiography (BSE) certifications. Currently, the BSE promotes quality echo systems in primary and secondary care, and provides accreditation pathways for GPs to gain formal accreditation and demonstrate ongoing exposure to maintain proficiency. Broadening the access to echocardiography in primary care could potentially improve the accessibility to specialist input and in turn expedite decisions for implementing treatment. This would also help to alleviate pressure on the current workforce, with one healthcare professional the APPG heard from during an evidence session, stating that workforce issues also had a significant impact on access to echocardiography, with more specialists needing to be recruited to keep up with demand. To highlight this issue, a 2016 study was referenced which stated that the UK required between 800 – 1,000 new echocardiographers to be trained over the next 4 to 5 years (Oakley. P. Improving Cardiac Care: Developing the Echo Service CSO's Policy Programme: Managing Service Demand and Transforming the Service Delivery Model Modelling	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the Future Workforce in Cardiac Physiology), a figure which is likely to rise due to the backlog in diagnostic testing caused by the COVID-19 pandemic.	
All Party Parliamentary Group on Heart Valve Disease	Guideline	016	009 - 010	During the APPG evidence session the importance of multidisciplinary teams in helping to advise patients regarding treatment decisions, specialist advice and general support was discussed. The APPG notes that MDTs are not mentioned within the draft guideline, however these teams would provide an ideal specialist point of contact for patients between appointments, as they could provide specific knowledge, explaining the different treatment options (surgical, TAVI, minimally invasive etc.) to patients as well as providing general support. During the pandemic, virtual MDTs were set-up and these should be continued, as this more agile approach will allow for faster decision making while services return to normal.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
All Party Parliamentary Group on Heart Valve Disease	Guideline	016	011 - 012	It's positive to see that the guideline calls for a consideration for providing psychological support for people receiving a diagnosis of valve disease, whether or not they have symptoms. Many of the patient representatives the APPG heard from during the oral evidence session stated that the treatment and diagnosis had a significant impact on their mental health, with one patient noting that they had "really struggled" due to delays in treatment. However, the APPG also heard from a number of patients who outlined that they had great difficulty trying to access rehabilitation services, a factor that also had a debilitating impact on their mental health. This impact however was often not realised until after support had been received. Given that this experience was shared by many of the patient representatives the APPG heard from, it clearly indicates that more needs to be done to address the ease of access patient's face.	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
All Party Parliamentary Group on Heart Valve Disease	Guideline	016	013 - 014	Following feedback received from healthcare professionals, it was found that the provision of detailed information to patients regarding their surveillance regime post-intervention was important, as well as providing a list of reliable sources that patients could utilise to seek answers to specific questions they may have. On this last point, many of the patient advocacy group representatives the APPG heard from concurred with the need to provide more direction to a few legitimate sources, such as the NHS, Heart Valve Voice and British Heart Foundation websites, as a way to prevent so called "google health" where patients search for their conditions or symptoms online and receive inaccurate information from non-trustworthy sites. The use of modern technology, such as specialist apps was also considered as an effective way to relay this information, and it was proposed that this could include a series of "red flag" symptoms that patients and their families would need to alert their GP to in the future. To ensure that all sections of the community were able to access relevant patient information all patient materials should be provided in multiple languages to ensure widespread accessibility, as well as ensuring availability in primary care settings as well as online.	Thank you for your comment. We have added the importance of providing information to patients regarding their surveillance regime post-intervention to the committee's discussion of the evidence in evidence review L. Recommendation 1.9.1 signpost to the NICE guideline on Patient experience of adult NHS services. This contains recommendations on information including advising the patient where they might find reliable high-quality information and support after consultations, from sources such as national and local support groups, networks and information services (1.5.18).
All Party Parliamentary Group on Heart Valve Disease	Guideline	019	009 - 011	After listening to the patient representatives, the APPG found that many adults with heart valve disease had to undertake a significant amount of independent research on the condition themselves, with the British Heart Foundation and Heart Valve Voice websites being identified as specific sources utilised. Patient's appreciated that these websites allowed for various forms of support e.g. videos and patient stories to be held in one place, reducing the need to undertake extensive research. The importance of social media groups was also highlighted as a way for patients to interact	Thank you for your comment. We cross-refer to the patient experience guidelines which advises the patient where they might find reliable high-quality information and support after consultations, from sources such as national and local support groups,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				with others in similar positions. In particular, the way that social media groups allow for the exchange of information and advice, as well as general support was praised. Overall, there was a consensus amongst the group that patient choice was extremely important to them. It is therefore recommended that the guideline committee considers the views of patients in this regard, ensuring that information and support is easily accessible with perhaps there being closer alignment between some of the key patient organisations operating in this space and the NHS. To ensure that patients know which sites to trust, it could be worth exploring the 'kite marking' of sources of information, which is being explored by the Patient Information Forum.	networks and information services. (Recommendation 1.5.18)
All Party Parliamentary Group on Heart Valve Disease	Guideline	021	014	During the APPG on HVD evidence session, healthcare professionals noted that even where patients do not need to be referred for interventions, ensuring that specialist GPs are responsible for the management of the condition is a useful way to ensure that patients are referred at the optimal time. Once referral has occurred, heart valve clinics were offered as an example of how clinical nurse specialists and physiologists can take on additional responsibilities, by running these clinics and ensuring that pressure can be taken off surgeons and echocardiography consultants. As such, as part of a research question into 'monitoring where there is no current need for intervention', it would be worth exploring the value of establishing further valve clinics across the UK to secure stronger links between the patient's GP and valve surgeon to enable a joined-up monitoring process.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite heart valve clinics as an example of how this may be provided.
All Party Parliamentary	Guideline	035	007 - 010	The APPG supports the committee's finding regarding the importance of shared decision making when discussing interventions, however it would implore the committee to consider the role of the MDT in regards to the	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Group on Heart Valve Disease				"sharing" of information and opinions between clinical experts. This is to ensure a holistic view of the patient pathway and that treatment options are fully explored, along with their risks and benefits. On patients specifically, it was found during the APPG's evidence session that they often felt confused or unsure regarding the treatment options available to them, outlining that not all treatment and therapy options were discussed with them, including minimally invasive surgery and transcatheter therapies. Equity of access to treatments, when appropriate, must be considered as part of this move to encourage shared decision making to ensure that patients receive the right treatment for them as well as the necessary information so that informed decisions can be made.	of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
All Party Parliamentary Group on Heart Valve Disease	Guideline	049	012 - 014	To ensure that all adults with heart valve disease have a point of contact between appointments or psychological support it was discussed during the APPG evidence session that establishing a support network of expert patients would be an effective way of providing support to adults who were newly diagnosed as they make their way through the patient pathway. These experts could then help to train the next generation and help to ensure that patients are able to pose questions to someone with the same lived experience, as well as having access to information online or at their GP surgery. Such a system could lead to the establishment of clinical champions that could be positioned in a range of communities to ensure that the variation in optimal care provided across the country can be minimised. The charity Heart Valve Voice has begun to establish a group of clinical patient champions who are based across the country and perhaps with engagement from the NHS, further champions could be established, with formal training and backing supplied by an organisation such as NHS England.	Thank you for your comment. We have added that support could also be provided by establishing a support network of expert patients to the committee's discussion of the evidence in evidence review L.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Barts Health NHS Trust	Evidence reviews	General	General	Serious concerns in the surgical community surround the following (see comments 1-4 below): 1. The use of primary end points favoring the percutaneous approaches. For example, in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) MitraClip trial, blood transfusion was included in the composite end point, weighted equally with mortality and stroke. 2. Reporting outcomes after relatively short follow-up to facilitate earlier regulatory approval, a strategy which favors the least invasive option and minimizes the opportunity to observe how incomplete or ineffective treatment affects long-term survival and quality of life. 3. The use of a non-inferiority trial design which makes it is easier (requires less efficacy and fewer patients) to show that outcomes are not significantly worse than to demonstrate that they are significantly better. 4. Many trials do not represent 'real world practice' with many patients excluded and yet findings are frequently extrapolated to a much wider population. This research is perceived then to unduly influence subsequent guidelines which tend to be written by clinicians who may have significant conflicts of interests. This introduces significant bias in the evidence base and undermines the confidence of both patients and clinicians. (Analysis of conflicts of interest among authors and researchers of European clinical guidelines in cardiovascular medicine. Jonathan Hinton, Thomas Reeves and Benoy Shah Clinical Medicine 2021 Vol 21, No 2: e166–70).	Thank you for your comment. 1. The protocol for this review was developed as a committee, with the discussion involving input from professionals with different areas of expertise, including those experienced in surgery and TAVI. Where possible, our review reported outcomes individually rather than composite outcomes that studies had reported as their primary outcome. 2. The time-point at which outcomes were reported was discussed as part of protocol development, with the longest possible follow-up sought for outcomes such as mortality and quality of life and shorter time-point of 30 days for other outcomes where the aim was to identify more immediate procedural-related events,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In December 2019, The European Association for Cardio-Thoracic Surgery (EACTS) withdrew support from the 2018 EACTS-European Society of Cardiology (ESC) Clinical Guidelines for Myocardial Revascularization after an investigative news report, and subsequent clinical data which emerged raised questions about reported outcomes from the EXCEL trial (BMJ 2019;367:l7006 Surgical association withdraws support for stent advice after controversy over study). In February 2020 The Latin American Association of Cardiac and Endovascular Surgery (LACES) similarly withdrew support from the 2020 AHA/ACC guidelines for the management of heart valve disease, releasing the following statement after publication: 'Guidelines on management of cardiovascular disease are constructed based on the best clinical evidence. We believe the recently released AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease 2020 have important sections which fail on this major premise and therefore our association will not support them'. The full statement and rationale were published as referenced. (The Latin American Association of Cardiac and Endovascular Surgery statement regarding the recently released 2020 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease Eur J Cardiothorac Surg 2021 Feb 12;ezab027. doi: 10.1093/ejcts/ezab027.) NICE is recognized internationally and nationally, across the whole profession and importantly by patients as having the highest standards in	such as atrial fibrillation and major vascular complications. 3. The sample size for each outcome once studies have been pooled would be taken into account in the quality assessment process, as imprecision is one of the factors assessed using GRADE and is generally increased when sample sizes are smaller. 4. In terms of real-world data, it may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-interventions comparisons. However, it should be emphasised that randomised efficacy data present an idealised estimate of true effectiveness, and it is usually implausible that any

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				producing guidelines and so this publication is timely and will restore confidence in professionals and patients.	differences between experimental and real-world settings would act to underestimate an intervention's 'true' effectiveness. Hence, preference will always be for high-quality randomised evidence when it comes to estimating the relative effects of different courses of action. Real world evidence may be considered if no or limited RCT evidence had been found. Cohort studies were not included also for this reason and for the difficulty of controlling for confounders.
Barts Health NHS Trust	General	General	General	Perhaps most importantly the guidance flies in the face of current clinical guidelines and if published in this form would place physicians and patients at variance with those commissioning healthcare.	Thank you for your comment. The guidance was produced in accordance with current NICE methods as described in the guideline manual https://www.nice.org.uk/process/pmg20/chapter/introduction. One of the main differences between NICE guidelines and other clinical

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					guidelines is the consideration of cost effectiveness and the resource impact of recommendations. We have revised these recommendations in the light of comments from stakeholders and revisions to the health economic model. For example have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).
Barts Health NHS Trust	General	General	TAVI v surgery	It takes no account of multidisciplinary working and shared decision making between patients and their doctors.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The importance of shared decision-making has been emphasised in the recommendations under 'decisions about interventions, with reference to shared decision-making as part of the NICE guideline on patient experience in adult NHS services made.
Barts Health NHS Trust	General	General	TAVI v surgery	It takes no account of the disutility of surgical intervention.	Thank you for your comment. The disutility of surgical intervention was accounted for in the economic model. In section 2.3.5.1 table 13 shows that people undergoing surgery have a lower quality of life during the first year after the intervention, due to the slower and harder recovery. This is true for people at low, intermediate or high risk alike.
Barts Health NHS Trust	General	General	TAVI v surgery	It does not differentiate between the use of mechanical valves and bioprosthetic valve and quantify the long term, risks, costs and disutility from mechanical valves.	Thank you for your comment. The comparison between mechanical and bioprosthetic valves in surgical valve replacement was not prioritised for review within the guideline. Therefore, we are unable to make recommendations in this area.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Barts Health NHS Trust	General	General	General	Linkage of data to routinely collected NHS data for long term outcomes would further improve the guideline. Currently the many diverse national data audits administered either by National Institute for Cardiac Outcome Research or individual professional bodies are limited to data during hospital admission. Linkage of the data to routinely collected NHA data such as Primary Care Data, Health Episode Statistics data or Data from the National Death Registry. This means it's often difficult to get data on the impact of decision about diagnosis and treatment of valve disease across the patients and across the NHS as whole.	Thank you for your comment. One of the main challenges to the model was the extrapolation of long-term data and outcomes, which were not provided by NICOR or other short-term audits such as NACSA. Some studies followed TAVI patients for a long period of time to derive mortality or dialysis outcomes, such as Martin 2017 and were therefore used in the model. The only downside of this approach is that these studies are often based on older datasets and may not reflect contemporary outcomes. However, we have addressed this issue through sensitivity analysis. In one of the deterministic analyses, we assumed that low risk people have the same mortality of the general population, to account for possible survival benefits due to more recent valves. This did not change the overall results of the analysis.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Barts Health NHS Trust	General	General	General	Guidance on the length of the pathway for severe symptomatic disease would further improve the guideline. There are many patients who wait months on waiting lists for definitive treatment of severe symptomatic heart valve disease. Delaying definitive treatment increases the risks of deterioration of left ventricular function, heart failure, hospitalisation and death. There have been many reports of this occurring especially on TAVI waiting lists as increasing number of patients have been diverted to TAVI treatment. In the NHS there are several examples where there are national guidelines in place to limit the time taken form referral to diagnosis and diagnosis to intervention. Management of patients presenting with red flag symptoms of cancer would be such an example. This may be an opportunity to provide guidance on the length of the pathway for patients with severe symptomatic heart valve disease.	Thank you for your comment. We have included referral times in the relevant recommendations in sections 1.1 and 1.4. The length of the entire pathway from diagnosis to treatment varies due to a large number of factors and it was not possible for the committee to make a consensus recommendation.
Barts Health NHS Trust	Guideline	004	004	Recommendation 1.1.1 and 1.1.2 The clinical criteria for referral for echocardiography are vague and contradictory. Clinical examination is a notoriously imprecise means of establishing the presence of underlying valve disease. It is a skill for which there is a wide variability in skills. There is a danger of underdiagnosis in setting conditionality.	Thank you for your comment. The committee considered that the health professionals who conduct the clinical examination would have the necessary skills to detect a murmur these include people working in A and E and non-cardiac specialities as well as GPs. The recommendation does not preclude a person being referred if heart valve disease is suspected in the absence of the absence of a murmur.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Barts Health NHS Trust	Guideline	005	002	Recommendation 1.1.3 The evidence separating 4 weeks for syncope is not explained satisfactorily and there is a strong case for acute admission of a patient with a load murmur and exertional syncope.	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks
Barts Health NHS Trust	Guideline	005	017	Recommendation 1.1.6 Mild aortic stenosis progresses frequently to severe aortic stenosis, the time frame is variable, and reassurance as opposed to programmed follow up is not appropriate.	Thank you for your comment. The committee have made a new recommendation to monitor people with mild to moderate valve disease every 3-5 yrs (1.4.2).
Barts Health NHS Trust	Guideline	006	General	We feel pregnant women with bioprosthetic valves not just those with mechanical valves either planning pregnancy or who are pregnant should undergo echocardiography (most likely within a maternal obstetric clinic). Given the haemodynamic changes during pregnancy baseline and serial echocardiography helps the clinician understand if gradients across the valve are consistent with the physiology of pregnancy or in fact represent pathological of the valve.	Thank you for your comment. We now refer to prosthetic valves and not just mechanical.
Barts Health NHS Trust	Guideline	006	001-004	The recommendation for specialist assessment applies to patients with mitral valve prolapse and documented arrhythmia. There is emerging evidence that patient with mitral annular disjunction are high risk for sudden death and arrhythmia; we would therefore feel it is reasonable for patients displaying these features including pickelhaube sign to remain under follow-up even in the absence of documented arrhythmia.	Thank you for your comment. After further discussion we have removed documented ventricular arrythmia from recommendation 1.1.7. This is because any patient with ventricular tachycardia would require assessment by a cardiologist, irrespective of the presence of mitral valve prolapse, the indication would be the arrhythmia, and not the mitral valve prolapse so it

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					was not appropriate to include this within this guideline. Similarly, the evidence regarding mitral annular disjunction is not yet sufficient to support a recommendation within a NICE guideline.
Barts Health NHS Trust	Guideline	008	General	The recommendation of when to intervene in patients with asymptomatic severe aortic stenosis differ to the 2017 ESC Valvular Heart Disease guidelines which many clinicians are familiar. Specifically the threshold for intervention is 5m/s rather than 5.5m/s and it is not clear the rationale for this. Also there is no documentation regarding the role of exercise testing in guiding intervention.	Thank you for your comment. The evidence showed that a peak aortic jet velocity more than 5 m/s was a risk factor for increased mortality (all-cause and cardiac or cardiovascular) and sudden death in people with asymptomatic severe aortic stenosis who had not had a valve intervention. There was no evidence to support the role of exercise testing in guiding intervention. As clinical practice is variable the committee were unable to make a consensus recommendation but did make research recommendations
Barts Health NHS Trust	Guideline	009	009 - 013	The recommendation for using ESDI 2.4cm2/m2 as a threshold to intervene in patients with asymptomatic severe aortic regurgitation is novel and not one many clinicians who follow the European Valvular Heart Disease Guidelines are familiar. We would argue that the conventional thresholds of LVEDD>70mm, LVESD>50mm (or 25mm/m2) which are well	Thank you for your comment. This choice of threshold was based on the best available evidence. Evidence showed an increased risk of left ventricular systolic dysfunction or death when ESDI was more than 24

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				established at our institution are appropriate and will maintain consistency within our practice.	mm/m^2. The committee also noted that the difference between 24 and 25 mm/m^2 was within measurement error and unlikely to make a practical difference.
Barts Health NHS Trust	Guideline	010	001	Mitral regurgitation - The guidance appears to suggest a course of action opposite to that of clinical evidence and current clinical guidance in recommending surgery for functional mitral regurgitation. Again these recommendations place physicians at variance with clinical guidance and open to criticism if they follow them and do not offer patients alternative strategies.	Thank you for your comment. We agree and have reworded the recommendation to reflect the originally intended meaning of referral for mitral valve repair surgery.
Barts Health NHS Trust	Guideline	010	005	The recommendation using ESDI 2.2cm2/m2 as a threshold to intervene on patients with asymptomatic severe mitral regurgitation is novel and not one many clinicians who follow the European Valvular Heart Disease Guidelines are familiar. We would argue that the conventional threshold of LVESVD>45mm which is well established at our institution is appropriate and will maintain consistency within our practice.	Thank you for your comment. We have edited recommendation 1.3.8 and now also refer to ESD more than 45mm.
Barts Health NHS Trust	Guideline	010	014	Recommendation 1.4.1 *Offer clinical review every 6 to 12 months, with an echocardiogram, to adults with asymptomatic severe valve disease if an intervention is suitable but not currently needed. Base the frequency of the review, within the 6- to 12-month timeframe, on echocardiography findings and discussion with the patient.* We strongly support the recommendation for regular monitoring in patients who have asymptomatic severe disease. However, we feel that new ways of working post pandemic may offer the opportunity for more regular clinical review of patients. We note that current ESC guidance suggests 6-month	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intervals for patients with severe asymptomatic valvular heart disease and wonder if there is an opportunity for earlier remote follow up especially for patients with severe disease. In addition recent data has suggested that early surgical intervention for asymptomatic aortic and mitral disease improves outcomes.	effective. Implementation of these should take the current context into account.
Barts Health NHS Trust	Guideline	011	016	Recommendation 1.5.2 *When surgery is agreed, base the decision on the type of surgery (median sternotomy or minimally invasive surgery) on patient characteristics and patient preferences. If minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre.* We welcome the recognition by the committee that minimally invasive surgery will play an increasing role in surgery for valve disease. It has become increasingly apparent that many patients prefer a minimally invasive approach over a sternotomy if they are suitable. Randomized controlled trials establishing the safety and efficacy of minimally invasive surgery for aortic valve surgery has been published in the UK and a large multi centre National Institute for Health care Research (HTA) funded trial in mitral valve surgery has recently completed recruitment. We recognize that the provision of minimally invasive valve surgery nationally is not uniform and support the recommendation that patients are offered the opportunity to move to other surgeons and other units with the expertise to provide this service.	Thank you for your comment.
Barts Health NHS Trust	Guideline	012	002-007	We are concerned there is clear definition of what makes surgery 'unsuitable' for severe AS. And regarding the rationale for surgery valve replacement over Transcatheter Aortic Valve Implantation the guidance references the following document 'Clinical Commissioning Policy: Transcatheter Aortic Valve Implantation (TAVI) For Aortic Stenosis 2013'.	Thank you for your comment. We have expanded on our definition of suitability for TAVI in the section 'terms used in this guideline' to make it clearer when TAVI is indicated for

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Since the publishing of this document there has been significant advances in percutaneous valve replacement, and we would argue this document no longer reflects clinical practice in high volume structural centres. Indeed this does not reflect the current ACC/AHA Valvular Heart Disease guidelines 2020 which states 'for symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability'. Our institutional practice for patients in this demographic to be counselled accordingly and discussed by the Heart Team. If the Heart Team believe both options are technically feasible with acceptable risk, then the patient is offered the option of both and has the option to choose either option. Although we appreciate surgical valve replacement offers a prognostic benefit in younger, fitter patients, our experience is transcatheter aortic valve implantation is an important alternative to those in whom co-morbidity makes surgery risk high. It also affords a quicker recovery time which is often preferable to some patients.	people unsuitable for surgery. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Barts Health NHS Trust	Guideline	012	003	Recommendation 1.5.3 *Offer surgery, if suitable (by median sternotomy or minimally invasive 3 surgery), as first-line intervention for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease.* We strongly support this recommendation. It is in keeping with outcomes nationally and in line with data published in the National Adult Cardiac Surgery Audit Summary Report of data from 2016/17-2018/19 published in 2020. (https://www.nicor.org.uk/national-cardiac-audit-programme/adult-cardiac-surgery-surgery-audit/).	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The audit highlights excellent outcomes for patients irrespective of age. In hospital mortality in patients over the age of 80 was 1.2% between 2016-2019. Similarly, the audit confirmed the relationship between risk and in hospital mortality. Contemporary outcomes in the UK are consistently lower than predicted risk scores, and in patients with the highest predicted in-hospital mortality (predicted risk of 8% or higher), mortality was only 5.6% in England. We support the fact that the document recognizes the clinical and cost effectiveness of surgery for the management of heart valve disease even in the elderly and that it highlights the role of minimal access surgery to improve choices for patients and potentially improve outcomes further. We support the emphasis that the committee has placed on long term clinical and QOL outcomes as well as the emphasis on long term and durable clinical benefit. We stress the role of the multidisciplinary team in the aspects of our response. Input from the MDT about risks not captured in standardised scores e.g. frailty, dementia, and complications other than mortality (e.g. para valvular leaks, pacemaker insertion or patient prosthesis mismatch) will make sure that decision making is patient focused. These complications are often associated with poorer quality of life and or long term survival.	NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Barts Health NHS Trust	Guideline	012	006	Recommendation 1.5.4 *Offer TAVI, if suitable, to adults with non-bicuspid severe aortic stenosis, if surgery is unsuitable.* The document recognizes the clinical and cost effectiveness of surgery for the management of heart valve disease even in the elderly. However, there are significant numbers of patients with severe symptomatic aortic stenosis who are not suitable for surgical intervention. The emergence of TAVI represents an opportunity to treat those patients. It's important that selection of patients for this technique is made in a multidisciplinary team and that surgeons get the opportunity to assess patients for suitability of surgery prior to transcatheter intervention. Similarly, it is important that patients get the option to meet a cardiac surgeon to discuss options. Frequently patients are anxious about surgery and are influenced by TV, social media, friends and other clinicians and the opportunity to meet a surgeon prior to making a decision is often very useful.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Barts Health NHS Trust	Guideline	013	004	Recommendation 1.5.8 Primary mitral regurgitation *Offer surgical mitral valve repair (by median sternotomy or minimally invasive surgery) to adults with severe primary mitral regurgitation and an indication for repair, if surgery is suitable.* We strongly support this recommendation which is in line with clinical evidence accrued over several decades. However, data from National Adult Cardiac Surgery Audit (NACSA) and for Getting It Right First Time (GIRFT) confirm significant variation in repair rates for PMR nationally. NICE should be more explicit about the need for patients to be referred to a suitably experienced specialist surgeon or centre.	Thank you for your comment. NICE guidelines are based on the assumption that the person carrying out the recommendation has the necessary expertise to so.
Barts Health NHS Trust	Guideline	013	011	Recommendation 1.5.10 *Consider transcatheter edge-to-edge repair, if suitable, for adults with 11 severe primary mitral regurgitation and symptoms, if surgery is unsuitable* There are significant numbers of patients with severe symptomatic mitral regurgitation who are not suitable for surgical intervention. The emergence of transcatheter edge-to-edge repair therapy represents an opportunity to treat those patients. It's important that selection of patients for this technique is made in a multidisciplinary team and that surgeons get the	Thank you for your comment. The recommendation specifies that the intervention should be offered only to patients deemed unsuitable for surgery. It is therefore crucial that a surgeon makes his/her assessment on suitability before referring the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				opportunity to assess patients for suitability of surgery prior to transcatheter edge-to-edge intervention.	patient to transcatheter edge-to-edge repair.
Barts Health NHS Trust	Guideline	014	003 - 005	Whilst we agree that all patients with secondary MR should be on optimised guideline directed medical therapy, there is emerging evidence both anecdotally and from detailed review of COAPT and the Mitra-FR studies, that there is a distinct cohort of patients with 'disproportionate' secondary mitral regurgitation who may benefit from edge to edge repair. We agree patients with mitral regurgitation which is proportionate to the degree of impairment of the left ventricle are not likely to infer prognostic benefit from edge to edge repair. We therefore feel this is a important development and therefore the distinction between 'proportionate' and 'disproportionate' mitral regurgitation should be included in this guideline with edge to edge repair being a consideration for those with disproportionate mitral regurgitation in whom surgery is not suitable.	Thank you for your comment. Transcatheter edge to edge repair may still be considered but after medical management has been tried first. We have added a recommendation to make this clearer 1.5.14. The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management.
Barts Health NHS Trust	Guideline	036 - 038	TAVI v surgery	The guidelines are based on an analysis of data from RCTs some of which are now 10 years old. They therefore do not reflect current practice in the UK and the very significant changes that have taken place in TAVI with reduced morbidity,	Thank you for your comments. The economic model was revised to derive data only from recent trials

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patient length of stay and enhanced recovery with less post hospital costs. These improvements translate into very real economic benefits which have not been accounted for.	reflecting outcomes of new generations valves. Moreover, several inputs are taken now from UK sources such as UK TAVI trial for LOS and ICU. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Barts Health NHS Trust	Guideline	General	General	In the guideline there is no specific mention of the 'Heart Team' and their input in decision making in patients with valvular heart disease. As a high volume centre we feel the input of the Heart Team at multidisciplinary meetings aids shared decision making and reflects best practice.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Barts Health NHS Trust	Guideline	General	General	Both physician and physiology led valve clinics have become invaluable in the management of patients with valvular heart disease who require surveillance and at our institution has improved and streamlined the management of our patients. These services are not mentioned in the guideline and we feel it would be important for their role to be included.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.
Barts Health NHS Trust	Guideline	General	General	I will make just a few points which I am sure others have also made. The document while being very lengthy appears to have been largely written by individuals following a formula but with no context on how valve disease is treated in the real world. The outputs are largely driven by the limited and out of date inputs leading to conclusions which are not relevant and not safe.	Thank you for your comment. The members of the committee were all health professionals working in the NHS and included two lay members in accordance with NICE methods https://www.nice.org.uk/process/pmg20/chapter/introduction. All relevant evidence meeting the review protocol criteria was included in the evidence reviews. The recommendations are based on clinical and cost effectiveness and aim to improve patient outcomes. The committee's clinical experience and knowledge

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					were also taken into account when formulating the recommendations. The model was revised to use contemporary and relevant data such as the recent UK TAVI trial and the latest NICOR TAVI and NACSA surgery audits.
Barts Health NHS Trust	Guideline	General	TAVI v surgery	Most TAVI now utilises no intensive care and the benefits of this have been highlighted during the COVID pandemic	Thank you for your comment. The model was revised to reflect contemporary practice regarding ICU need after TAVI. Data now come from the recent UK TAVI trial and the model assumes no ICU needed after TAVI. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Barts Health NHS Trust	Guideline	General	TAVI v surgery	TAVI valve costs are based on list prices. These are artificially high as actual price paid can be much lower when volume discounts are taken into consideration	Thank you for your comment. The model was revised to use the price reported by the NHS Supply Chain under the NHSE High-Cost Tariff Excluded Devices Programme: £17,500. This is a price across the volume and represents the average price 80% of TAVI valves are purchased in the NHS. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Barts Health	Guideline	General	TAVI v	There is no reliable data that TAVI valves overall are less durable than surgical bioprosthetic valves.	Thank you for your comment. We have amended the committee's discussion of the evidence in

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Trust			surgery		evidence review H. We now refer to limited evidence of TAVI valve durability, only up to 6-7 yrs.
Barts Health NHS Trust	Guideline	General	General	We support all the main recommendations of the draft document. These recommendations will significantly improve access to care, timely diagnosis, appropriate intervention and outcomes both short and long term, for patients with heart valve disease. The NICE guidelines are a timely document and is published at time that confidence in guidelines issued by The American College of Cardiology and European Society of Cardiology have become increasing strained. In the cardiovascular device arena in particular, it has become apparent that research is frequently designed, funded and the findings interpreted by device companies in order to achieve regulatory approval.	Thank you for your comment.
Barts Health NHS Trust	Guideline	General	General	Recognition of the impact of the Heart team in decision making would further improve the guideline. Multidisciplinary teams (MDT) have become increasingly important in the management of heart valve disease. This document highlights complexities in the diagnosis, management (medical and intervention) and long term follow up of valve heart disease patients. These decisions need to be taken within the setting of the multidisciplinary team. The MDT brings specialists together, usually within the setting of a multi-disciplinary meeting (MDM), with knowledge, skills and experience to interpret results, discuss diagnostic and therapeutic options, to help the patient decide on their preferred treatment. The recommendations made in these guidelines (e.g. Indications for intervention in patients with asymptomatic severe aortic	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. Thank you for your comment regarding the rapid evolution of virtual technology during the Covid 19 pandemic.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				stenosis,1.3.2 or Mitral valve repair for primary mitral valve regurgitation, 1.5.8) are most likely to be implemented in an MDT setting. The rapid evolution of virtual technology during the Covid 19 pandemic has facilitated much wider involvement of all clinicians in the network in the MDM process. In the future it may also allow for the involvement of patients and relatives either 'live' or in the form of records of video consultation bringing patients closer to the decisions made about them.	
Barts Health NHS Trust	Guideline	General	General	Amalgamation of current national data sets into disease specific databases would further improve the guideline. The documents alluded to the presence of several national databases for heart valve intervention. The UK TAVI dataset and The National Adult Cardiac Surgery Audit data are the largest but there are other datasets for balloon valvuloplasty, edge to edge percutaneous therapies etc. There is an urgent need for these registries to be joined up as single registries covering intervention on specific valves e.g. an aortic valve intervention registry capturing all intervention on the aortic valve including, surgery, TAVI, valvuloplasty etc. This will allow all professions and patients to audit outcomes in a much more meaningful way.	Thank you for your comment. The committee acknowledge the importance of collecting outcome data (see the committee's discussion of the evidence in evidence review H) however, NICE guidelines are unable to recommend how this data is collected.
Blackpool Teaching Hospital	Economic report TAVI	026		The NHS reference cost figures for TAVI are higher than PLICs sent through by Trusts carrying out TAVI (eg our centres average PLIC figure for TAVI is £5620.	Thank you for your comment. We revised our approach to use UK source instead of US-based trials to estimate Length of hospital stay and ICU stay after TAVI and SAVR.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
s NHS Trust					Consequently, our estimation of costs of a TAVI procedure has changed. The costs of a TAVI procedure for all risk groups (without the valve) are now estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates seem to be in line with the cost reported in your institution. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Blackpool Teaching Hospitals NHS Trust	Economic report TAVI	027		ICU & LOS stay figures do not represent current practice: Our transfemoral TAVI patient have zero ICU stay and our median LOS for all our TAVI patients is 1 (approx 15% of our transfemoral TAVI cases over the 12 months have been same day discharges)	Thank you for your comment. After further discussion, the committee agreed to use UK data for LOS and ICU LOS as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Blackpool Teaching Hospitals NHS Trust	Economic report TAVI	029	010	The largest cost element to a TAVI procedure is the device cost (£20280) – as acknowledged by the Committee this price is considerably higher than that paid in Germany or France: The whole purpose of centralised procurement of high cost devices was to reduce Unit prices of expensive devices such as TAVI & ICDs, yet NHS Supply Chain is till paying the same prices as 2 years ago and much higher than other European Countries. If NHS supply chain negotiated the price that Germany for example pays then TAVI for all aortic stenosis patients becomes cost effective!	Thank you for your comment. Indeed, the largest component of cost comes from the device (which was revised to £17,500 in the new version of the model). This is higher than the cost incurred by other countries e.g. £14,400 for Canada (https://www.dovepress.com/a-canadian-cost-effectiveness-analysis-of-sapien-3-transcatheter-aorti-peer-reviewed-fulltext-article-CEOR) and £12,000 for France (https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036577833).
Blackpool Teaching	Economic report TAVI	General		The studies used for cost utility analysis should reflect current practice and devices used in the UK eg Partner 3, Evolut Low Risk, UK-TAVI trial.The postprocedural outcomes used in the modelling are all much lower in the	Thank you for your comment. The model was revised to include only data on contemporary TAVI valves.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Hospitals NHS Trust				recent trials than in older TAVI trials that included older devices and more non transfemoral approaches.	The meta-analysis used in the base case scenario includes trials of 2nd and 3rd generation valves only: • PARTNER 2 • PARTNER 3 • Evolut UK TAVI trial effectiveness outcomes were not used as the paper is currently unpublished. However, descriptive statistics coming from this trial were used to estimate length of hospital stay and ICU stay in low-risk patients. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Blackpool Teaching Hospitals NHS Trust	Guideline	005	002 - 015	We would fully support the need for urgent echocardiogram and access to specialist assessment. However this would be challenging to implement without additional resource. However there may be a way to facilitate rapid uptake, namely augmentation of the rapid acute HF diagnostic clinics that have been set up throughout the country following the NICE guidelines for CHF (rather than setting up separate rapid diagnostic clinics for valular heart disease patients) . The majority of undiagnosed valve disease patient do present with symptoms (shortness of breath, fatigue) and signs (peripheral oedema etc) of heart failure .	Thank you for your comment. Service delivery including acute HF diagnostic clinics were not included in the scope of this guideline.
Blackpool Teaching Hospitals NHS Trust	Guideline	008	006 - 013	We fully support earlier intervention in "higher risk" asymptomatic severe aortic stenosis patients and agree with the criteria recommended but would suggest adding mid wall fibrosis on cardiac MRI to the list since these individuals have been shown to have poorer outcomes.	Thank you for your comment. Most of the evidence suggested that myocardial fibrosis was associated with increased risk of a poor outcome in severe aortic stenosis. This was in line with the committee's experience that myocardial fibrosis in general, not only in aortic stenosis, is associated with a worse prognosis. Furthermore, myocardial fibrosis in people with severe aortic stenosis indicates early decompensation and the possible need for early intervention to stop progression, because midwall fibrosis cannot be reversed or improved by

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					intervention. The committee agreed that follow up should be enhanced and further assessment should be offered in those with midwall fibrosis to check for symptoms and enable earlier aortic valve intervention to improve prognosis (See recommendation 1.3.6)
Blackpool Teaching Hospitals NHS Trust	Guideline	011	005 - 012	We feel there needs to be a line regarding "potential catheter based intervention" since this will be applicable for some of the patients.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). We now therefore refer to transcatheter in recommendation 1.3.8 as it is an option for people at high surgical risk.
Blackpool Teaching Hospital	Guideline	011	016 - 019	We fully support the concept of referring to another centre patients for minimally invasive surgery if not available locally, if this is deemed the appropriate treatment after discussion between surgeon and patient. We have a well established minimally invasive service (for both mitral and aortic valve interventions) at BTH and already receive referrals from other centres and have capacity to increase such referrals.	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
s NHS Trust					
Blackpool Teaching Hospitals NHS Trust	Guideline	012	003 - 012	Our Unit has a well established MDT decision making process for patients with significant aortic valve disease for determining valve intervention and type of intervention (SAVR or TAVI) – this includes input from the patient. This is standard practice throughout most of the country and thus lines 3-5 are contrary to current practice, Specialist Society guidelines (International and National), NHS clinical commissioning and NICE's own interventional guidance on transcatheter aortic valve implantation for aortic stenosis.	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). We have added a cross reference to the NICE guideline on shared decision making to recommendation 1.5.1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Blackpool Teaching Hospitals NHS Trust	Guideline	012 036	006 026	TAVI has been shown to produce good outcomes in bicuspid patients (eg data from the STS/ACC TVT registry published in Feb 2020, Circulation)	The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included studies meeting the review protocol criteria (see Appendix A). In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.
Blackpool Teaching Hospitals NHS Trust	Guideline	014	003 - 005	This part of the guidance needs to be modified, such that transcatheter mitral edge to edge repair is considered in this patient. The most current trial on severe secondary MR (COAPT) with LV impairment has demonstrated significant benefit (hospitalisation with heart failure reduced by more than 50% over 24 month period and death reduced by almost 40%) with use of mitral E-E repair compared to optimal medical therapy alone.	Thank you for your comment. Transcatheter edge to edge repair may still be considered but after medical management has been tried first. We have added a recommendation to make this clearer (1.5.14). The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management.
Blackpool Teaching Hospitals NHS Trust	Guideline	017	021	3D ICE catheter can be used in patients who are unable to have transoesophageal echo	Thank you for your comment. No evidence was found on ICE catheter and the committee were therefore unable to make a recommendation.
Blackpool Teaching Hospitals NHS Trust	Guideline	036	010 - 013	The more contemporaneous trials using more recent iterations of TAVI valve (eg Partner 3, Evolut low risk) show no increase in mortality (possible decrease), reintervention, rehospitalisation) compared to surgery.	Thank you for your comment. The design of the review in terms of pooling and stratification were discussed at length with the committee during the development of the review protocol. It was agreed that studies comparing transcatheter intervention with surgical intervention would be combined initially, regardless of factors such as device generation and TAVI approach. However, it was agreed that for any outcomes where heterogeneity was present in the meta-analysis, the impact of certain factors that were

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					thought most likely to have an effect on outcome (including access route and operative risk, for example) on the outcome would be explored using subgroup analyses. Device generation or year of the trial was not prespecified in the protocol and therefore evidence could not be considered separately for this factor.
Blackpool Teaching Hospitals NHS Trust	Guideline	038	017	Patient choice is increasingly a factor in choice of intervention and does need to be mentioned here because it reflects current practice	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Boston Scientific	All	General	General	The COVID-19 pandemic has had a significant impact on the UK healthcare service. A recent modelling report estimated 4989 (95% CI 4020-5959) of Aortic stenosis patients had not received treatment in the period March – November 2020. Whilst some services can mitigate challenges such as the impact of treatment delay, Heart Valve disease cannot. • A recent modelling report on the impact on Cardiovascular waiting lists highlighted a mortality rate of 4% for people on the waiting list, with a range of 2-14%[1].	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• This equates into 99-698 deaths for patients waiting for intervention[1]. • This backlog may be further compounded by future waves and an ability to deliver historic volumes due to heightened PPE, social distancing and testing requirements. TAVI was an important element of service delivery during the first wave of the pandemic and offers several operational benefits that may help support service recovery and reduce elective backlog (NHS England 2020). We therefore ask the committee to review the following publication by Khialani & MacMarthy 2020 (heartjnl-2020-317221.pdf (nih.gov)] and consider the broader benefits of the TAVI procedure in this context. 1. Modelling Solutions to the Impact of COVID-19 on Cardiovascular Waiting Lists Tuesday 2nd – Thursday 4th February 2021 (newton.ac.uk) 2. NHS England and NHS Improvement. Clinical guide for the management of cardiology patients during the coronavirus pandemic. 20 March 2020. Available at: https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-guide-cardiolgy-coronavirus.pdf 3. Khialani B, MacCarthy P. Transcatheter management of severe aortic stenosis during the COVID-19 pandemic. Heart. 2020 Aug 1;106(15):1183-90.	should take the current context into account. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Boston Scientific	Economic Model	General	General	We do not believe the cost of the valve assumption used in the base case scenario is an accurate reflection of current UK price. We ask the	Thank you for your comment. The base case price has now been changed to reflect the actual price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				committee to use a value that more accurately reflects the UK ASP in its base case analysis.	valves are currently sold to the NHS at £17,500 This information comes directly from the NHS supply Chain so we consider it highly reliable and should reflect the true price NHS is currently purchasing the valves in the UK.
Boston Scientific	Economic Model	General	General	Hospital costs We do not believe the ICU and ward length of stay assumptions in the model reflect UK standard of care. They are based on outdated references from a non-UK setting and distort some of the procedural costs. Several references below highlight this. In the latest UK TAVI trial a median LOS of 3 days was reported in the TAVI group (0 day ICU) (Toff et al, 2020). A publication by Khialani & MacCarthy (2020) highlights the impact of advancements in TAVI procedures that have allowed for shorter inpatient hospital stays post-implantation. Specifically, they report a median LOS of 3 days in the UK and highlight the scope for further improvement through effective same day discharge programs. Furthermore, a publication by Ali et al (2021) shows the extent of the shift away from general anaesthesia and reports >95% of procedures are performed under local anaesthesia and the procedures were associated with a significantly reduced hospital stay, more rapid recovery and far less consumption of hospital resources.	Thank you for your comment. After further discussion, the committee agreed to use the UK TAVI trial instead of the data coming from the non-UK trials as the committee agreed that there is an important difference in practice among countries. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We request the committee incorporate LOS data that accurately reflects current UK practice. References • Toff WD. The United Kingdom transcatheter aortic valve implantation (UK TAVI) trial. InAmerican College of Cardiology Virtual Annual Scientific Session Together With World Congress of Cardiology (ACC 2020/WCC) 2020. • Ludman PF. Uk TAVI registry. Heart. 2019 Mar 1;105(Suppl 2):s2-5.. • Ali N, Faour A, Rawlins J, Dawkins S, Appleby CE, MacCarthy P, Byrne J, Trivedi U, Curzen N, Banning AP, Ludman P. 'Valve for Life': tackling the deficit in transcatheter treatment of heart valve disease in the UK. Open heart. 2021 Mar 1;8(1):e001547. • Khialani B, MacCarthy P. Transcatheter management of severe aortic stenosis during the COVID-19 pandemic. Heart. 2020 Aug 1;106(15):1183-90. Furthermore, we also question the assumption regarding LOS per day costs for SAVR and TAVI (£325 and £473 respectively). Given TAVI is a minimally invasive procedure we disagree with the assumption it is associated with higher per diem costs versus SAVR. We believe the use of excess bed days to calculate per diem costs is in this situation is	We are using the median LOS and ICU reported by UK TAVI trial (http://www.clinicaltrialresults.org/Slides/ACC%202020/UKTAVI_Toff.pdf) which were scaled for higher risk using the study on hospital resources from Reinhoul (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/) Regarding bed cost the revised model now uses for the TAVI arm the same bed day as applied to the SAVR arm.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				inappropriate and is biased against TAVI due to the greater percentage of inoperable & higher risk patients that will exist in this reference cost cohort versus SAVR. We ask the committee to consider applying the same per diem cost assumption.	
Boston Scientific	Economic Model	General	General	**Pacemaker cost assumptions** We believe the documented consideration of NICE, that pacemaker costs could be considered within the TAVI HRG is a more accurate representation of costs incurred by the payer and hospital and thus we propose this assumption is used in the base case analysis. The vast majority of pacemaker implantations occur within the same spell as the TAVI procedure and thus do not receive a specific HRG payment. We therefore believe it appropriate to assume these costs are captured in the TAVI HRG. If the committee maintain its position these costs should be captured separately, we suggest the committee: • Firstly, exclude biventricular pacemakers from there weighted average calculation as these relate to the treatment of heart failure and not typically used to address conduction issues secondary to TAVI intervention. • Secondly, adjust the reference cost so it is more reflective of care consumed. For example, these reference costs typically reflect the end to end cost of a pacemaker procedural spell; which is not reflective of pacemaker placement associated with TAVI. The current approach in our opinion double counts some elements of	Thank you for your comment. The committee agreed to assume that the short-term cost of all adverse events (major bleeding, vascular complication, pacemaker implantation) as already included in TAVI and SAVR HRGs in the base case scenario, so no cost is applied in the decision tree other than the intervention cost. We are including a sensitivity analysis where all the costs are instead counted separately but, as you suggested, we excluded biventricular pacemaker from the weighted average cost of pacemaker.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				care consumption e.g. bed days of the patient spell which is captured in both the TAVI reference costs and pacemaker costs.	
Boston Scientific	Economic Model	General	General	**Reintervention rates** We ask the committee to review its use of Ler et al 2020 when informing reintervention odd ratios in the economic model. In evidence review H, NICE conclude the methods used in this SLR and meta-analysis are not adequate/unclear, we therefore query its use in the economic model. Furthermore, the scope of the Ler et al 2020 analysis was restricted to evaluating mainly the outcomes of early-generation TAVR valves compared to SAVR valves. Valves from newer generations have been shown to have lower 5-year rate of SVD (Pibarot et al 2020). Reference Pibarot P, Ternacle J, Jaber WA, Salaun E, Dahou A, Asch FM, Weissman NJ, Rodriguez L, Xu K, Annabi MS, Guzzetti E. Structural deterioration of transcatheter versus surgical aortic valve bioprostheses in the PARTNER-2 trial. Journal of the American College of Cardiology. 2020 Oct 20;76(16):1830-43.	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review not using GRADE system, though it was included as evidence for the model, as the absence of GRADE system was not considered a severe limitation. Though, after a further committee discussion, it was agreed to exclude this evidence as it was clearly focused on old generation valves not reflecting contemporary practice, as your comment highlighted. Relative treatment effects for reintervention now come from the trials included in the literature review as these were extensively discussed and reviewed by the committee. In the base case we are only using the treatment effect captured in trials

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					evaluating 2nd and 3rd generation valves: • PARTNER 2 • PARTNER 3 • EVOLUT In addition, we added a sensitivity analysis where this figure is instead calculated from Evolut and Partner 3 only, with a relative risk close to 1. As a result of revision to the economic model based on stakeholder comments we have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Boston Scientific	Guideline	General	General	The role of the MDT in aortic valve interventions. We are concerned the wording of the current recommendations fails to acknowledge the role of the multi-disciplinary heart team (MDT) when selecting the most appropriate option for aortic stenosis. We ask the committee to place greater emphasis on the role of the MDT when deciding on the most appropriate valve therapy for patients. The below extracts from the recent Health Technology Wales TAVI HTA and NICE TAVI IPG both acknowledge the role of the MDT in their guidance and we ask the committee to consider this. *HTW extract:* *'The Appraisal Panel agreed that the choice between TAVI and SAVR should be undertaken by a multidisciplinary heart team and should be guided by detailed individualised assessment of risk factors, including age, frailty and other comorbidities. Where both TAVI and SAVR are an option, the multidisciplinary team should include both a cardiac surgeon and cardiologist.' (p3.)* GUI024-Transcatheter-Aortic-Valve-implantation-English.pdf (healthtechnology.wales) NICE IPG586 extract '*Patient selection should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the*	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				procedure, cardiac surgeons, an expert in cardiac imaging and, when appropriate, a cardiac anaesthetist and a specialist in elderly medicine. The multidisciplinary team should determine the risk level for each patient and the TAVI device most suitable for them' www.nice.org.uk/guidance/ipg586	
British and Irish Society for Minimally Invasive Cardiac Surgery				The British and Irish Society for Minimally Invasive Cardiac Surgery was formed in 2015 to promote the adoption of minimally invasive techniques in cardiac surgery so that more patients can be offered these innovative techniques. We value the opportunity to respond to the National Institute for Health and Care Excellence (NICE) draft guidelines on the investigation and management of heart valve disease. We support the main recommendations of the draft guidelines and, in particular, welcome the specific guidance to offer minimally invasive surgery to patients with aortic and mitral valve disease. However, we should note that pracice in the UK lags substantially behind our European neighbours. For example, in Germany in 2019, 53% of all isolated mitral valve surgery was performed using minimally invasive techniques, as compared to approximately 10% in the UK (Beckman et al. Thorac Cardiovasc Surg 2020 Jun 68(4);263-276). If we look at just degenerative mitral valve disease, that figure rises to 70%. Thus, we have more to achieve and these timely guidelines from NICE provide an opportunity to substantially benefit patients. NICE is recognised internationally, by clinicians and patients alike, as producing roboust evidence-based guidelines and we believe that there is	Thank you for your comment.

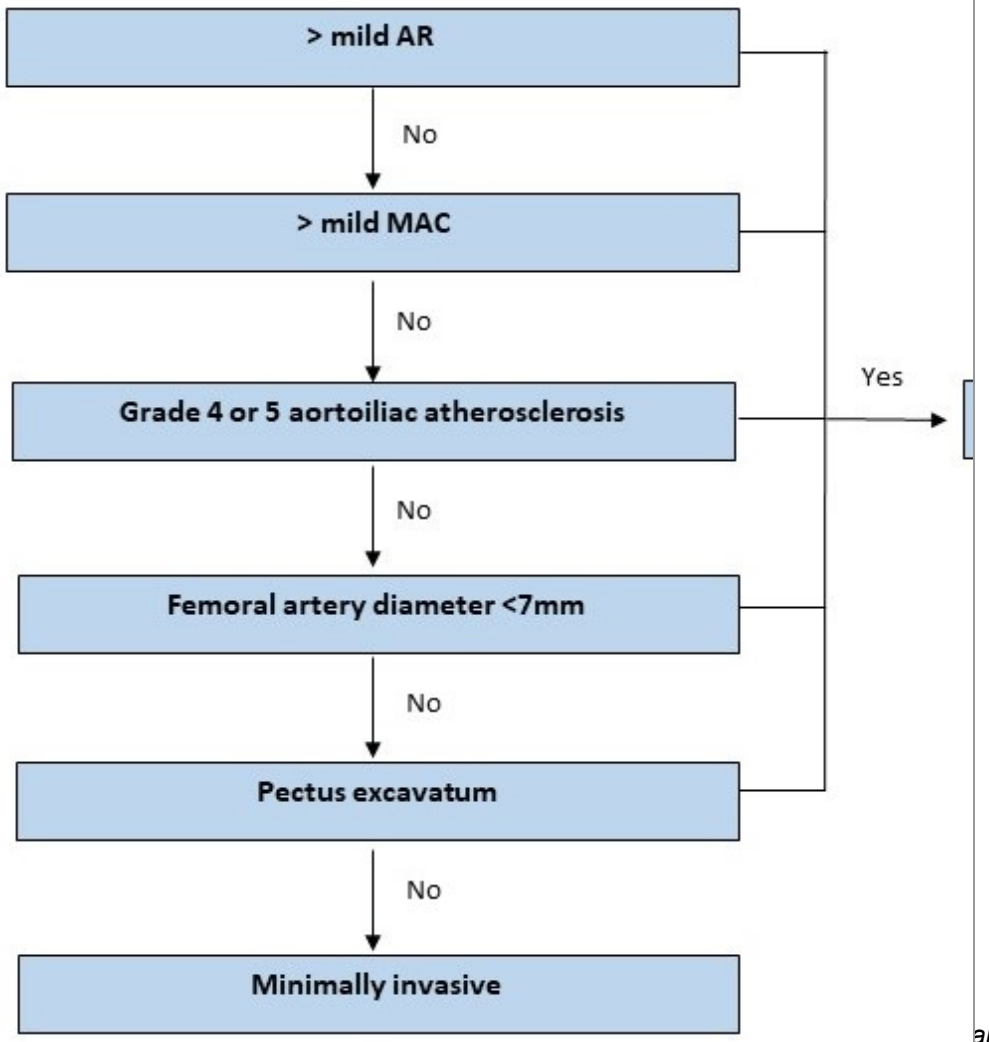
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				now a plethora of evidence supporting more widepsread adoption of minimally invasive surgery in the NHS, as has already happened in Europe and North America. This is heavily influenced by patient demand to avoid a sternotomy. To help us achieve this, the leadership of BISMICS offers fellowship training programmes and proctoring services to guide the introduction of minimally invasive cardiac surgical techniques into NHS institutions.	
British and Irish Society for Minimally Invasive Cardiac Surgery				**Surgery for atrial fibrillation (AF) concomitant with mitral valve disease** The development of the maze procedure by Dr Cox opened up a new therapeutic window for the surgical cure of AF. The classical cut-and-sew maze procedure performed through a sternotomy underwent various modifications and can now be performed using alternative energy sources (bipolar radiofrequency and cryothermy) through minimally invasive incisions giving equivalent results to Dr Cox's original procedure. The only RCT with longer follow up showed a significant reduction in stroke risk at 5 years and a greater likelihood of maintaining sinus rhythm (Osmancik P et al, *Heart Rhythm* 2019; 16:1334-1340). The largest registry published, from the Polish National Health Service, describes better survival when ablation is performed concomitant to mitral valve surgery (Suwalski P et al. JTCVS 2019 Mar;157(3):1007-1018). Analysis of 28,739 propensity matched pairs from the STS database showed a reduced risk of	Thank you for your comment. The management of AF and HVD with ablation was not included in the scope of this guideline. The NICE guideline on AF includes recommendations on ablation. Patients with heart valve disease were not excluded from the evidence review https://www.nice.org.uk/guidance/ng196.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				30-day mortality and stroke in those undergoing surgical ablation (Badhwar et al. Ann Thorac Surg 2017 Aug;104(2):493-500). Close cooperation between cardiac surgeons and electrophysiologists in a Heart Team is optimal. Up to one third of patients undergoing mitral valve surgery will have AF. Whilst surgical Pulmonary Vein Isolation (+/- isolation of the posterior LA wall) has been shown to be effective for maintaining sinus rhythm in paroxysmal AF, persistent and long-standing persistent AF require a more effective biatrial lesion set. The European Society of Cardiology gives concomitant AF ablation during MV surgery a class IIa recommendation (level of evidence A). BISMICS believes that the NICE Valve guidelines should specifically mention the treatment of concomitant AF during mitral valve surgery and that referral to a surgeon trained to perform the required lesion set should be considered, even if that is not available locally.	
British and Irish Society for Minimally Invasive	Guideline	010	002-011	BISMICS welcomes the recommendations detailed under section 1.3.8. Peri-operative risk is lower and long term survival is better for valve repair rather than replacement. It is now well established that repair rates and outcome are linked to surgeon volume, with higher volume surgeons having higher repair rates. This is important for all patients with degenerative mitral valve disease, but more so for those who are asymptomatic. Patients should therefore only be referred to high volume	Thank you for your comment. No evidence was identified on the level of expertise required to carry out the intervention and due to variation in current clinical practice a consensus recommendation could not be made.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Cardiac Surgery				(>20 cases per year) mitral surgeons with a demonstrated high repair rate with a low recurrence of >2+ MR. This is in the best interests of patients.	
British and Irish Society for Minimally Invasive Cardiac Surgery	Guideline	011	016 - 019	BISMICS welcomes recommendation 1.5.2, but it is not clear which clinician will opine on the most appropriate type of surgery (sternotomy vs minimally invasive). The referring cardiologist cannot be expected to have knowledge to make this decision. Clinicians will have a bias to interventions they are more familiar with. It is unequivocal that a multi-disciplinary Heart Team improves decision making. We therefore recommend that decisions about type of surgery are made in the Heart Team meeting with representation by both minimally invasive and conventional cardiac surgeons. When this is not possible, we suggest using the following flow chart: **Flow chart for referral for minimally invasive mitral valve surgery:** **(see next page)**	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The current recommendations do not preclude a referral to the MDT where available. The committee confirmed that it is important to highlight that patient characteristics and patient preferences should be taken into account when deciding on the type of surgery. Where appropriate the committee particularly wanted to highlight the importance of patient preferences and shared decision making.



Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British and Irish Society for Minimally Invasive Cardiac Surgery	Guideline	013	004 - 006	BISMICS welcomes the recommendation 1.5.8 to offer mitral valve repair by either median sternotomy or minimally invasive surgery to patients with severe primary regurgitation. However, as detailed in our response #2, clarity is needed over the decision making as to the most appropriate surgical approach that avoids individual surgeon bias for a particular procedure. This decision should either be made in a Heart Team with both minimally invasive and conventional cardiac surgeons represented, or a flowchart should be followed as detailed above.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The current recommendations do not preclude a referral to the MDT where available. Recommendation 1.9.4 covers the provision of information and advice on interventions and the committee support the importance of avoiding surgeon bias.
British and Irish Society for Minimally Invasive Cardiac Surgery	Guideline	013	007 - 010	This recommendation 1.5.9 states to offer valve replacement to severe primary mitral regurgitation if the valve is not suitable for repair. The majority of primary mitral regurgitation is due to degenerative disease and almost all degenerative valves can be repaired by suitably experienced surgeons. Repair has short- and long-term benefits over valve replacement, including a threefold lower operative risk and superior long-term survival. If the local surgeon feels he cannot offer a durable repair for a degenerative valve, the patient should be referred to another centre out-of-region for the necessary surgical expertise.	Thank you for your comment. The recommendation does not preclude a patient being referred to another centre for repair if this is appropriate.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British and Irish Society for Minimally Invasive Cardiac Surgery	Guideline	014	008 - 015	Recommendation 1.6.1 deals with repeat intervention and seems to be limited to bioprosthetic aortic structural valve degeneration. In reality, lines 12-15 also apply to bioprosthetic mitral valve degeneration. There is evidence that when the first cardiac procedure was performed through a sternotomy, then a reoperative minimally invasive mitral valve procedure performed through a right minithoracotomy reduces the chance of cardiac/graft injury and is safer for patients. We suggest adding the following – "*for mitral valve reoperations, when the first procedure was performed through a median sternotomy, a minimally invasive procedure should be considered if the decision is for redo surgical intervention".*	Thank you for your comment. No evidence was identified for the type of intervention you describe and therefore the committee were unable to make a recommendation. The committee also made research recommendations for repeat intervention for failing biological prosthetic aortic, mitral and tricuspid valves because the only available evidence was non-randomised.
British and Irish Society for Minimally Invasive Cardiac Surgery	Guideline	015	002 - 003	Recommendation 1.7.1 deals with anticoagulation after surgical biological valve replacement and states "***do not offer anticoagulation after surgical biological valve replacement unless there are other indications for anticoagulation".*** We are concerned that NICE are specifically recommending not to anticoagulate patients after bioprosthetic mitral valve replacement. This is contrary to the 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. There is evidence of reduced thromboembolic complications with anticoagulation, particularly for bioprosthetic mitral valves.	Thank you for your comment. No evidence was found to support a recommendation for anticoagulation in patients with bioprosthetic mitral or tricuspid valves. However, we agree that patients with mitral and or tricuspid valve disease in need of replacement have paroxysmal atrial fibrillation more often than not and atrial fibrillation is an indication for anticoagulation.
British and Irish Society for	Guideline	035	007 - 014	BISMICS welcomes the concept of shared decision making so that the risks and benefits of all treatment options are explored with patients. We disagree however that there is no difference between minimally invasive	Thank you for your comment and the reference citations. These studies cannot be included in the review as we limited to RCTs. The available

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Minimally Invasive Cardiac Surgery				and standard surgery in terms of outcomes when performed by those with expertise in minimally invasive surgery. There is recent evidence from the UK of superior **patient-reported outcomes** with minimally invasive surgery (Whiteley et al. Interactive CardioVasc Thorac Surg 2020) with equivalent safety (Grant et al Heart 2019;105(20):783-89).	randomised evidence suggested possible harms of minimally invasive surgery compared to standard surgery in aortic stenosis; but possible clinically benefits of minimally invasive surgery in mitral regurgitation. However, the evidence was of limited quality and quantity. The committee did not want to limit the use of minimally invasive surgery because in their experience this technique can have similar outcomes and has advantages for some patients. Therefore, both minimally invasive and standard surgery were recommended as options. There was insufficient randomised evidence to recommend minimally invasive surgery in preference to median sternotomy for any type of heart valve disease.
British and Irish Society for Minimally	Guideline	035	015 - 018	BISMICS welcomes the recommendation that a lack of expertise at the local centre should not be used as a reason for not performing minimally invasive surgery, and patients should be referred to a centre where the necessary surgical expertise is available. This is clearly in the best	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Invasive Cardiac Surgery				interests of patients and is concordant with the Montgomery case of 2015 and Informed Consent (BMJ 2017;357:j2224).	
British and Irish Society for Minimally Invasive Cardiac Surgery	Guideline	035	021 - 024	We believe that minimally invasive surgery will be suitable for the majority of patients undergoing isolated heart valve surgery. In Germany, 70% of patients having surgery for isolated degenerative mitral valve regurgitation have minimally invasive surgery, compared to only 10% in the UK. Most patients with isolated mitral valve disease are suitable for minimally invasive surgery by appropriately experienced high volume minimally invasive surgeons. Patient safety is equivalent to sternotomy whereas patient reported outcomes are superior, as detailed above. We would expect this change in practice to have a significant impact on current practice. ***"Those for whom it is suitable may decide not to opt for a minimally invasive surgery after considering the increased likelihood of failure of repair, needing redo surgery or other complications"*** - There is no published contemporary data that shows that minimally invasive surgery is associated with an increased likelihood of repair failure, reoperation or complications. In fact, there are numerous meta-analyses and propensity matched comparisons that have shown either equivalent or superior outcomes with minimally invasive surgery (Grant et al *Heart* 2019;105(20):783-89; Nissen et al *Ann Thorac Surg* 2021;111(3):819-27; Cheng et al *Innovations* 2011;6(2):84-103; Pompeu et al *J Card Surg*	Thank you for your comment. The section you refer to covers all types of heart valve disease, not just MR. It was agreed that in current practice, decisions between minimally invasive and standard surgery (median sternotomy) for surgical mitral valve procedures (repair or replacement) would be based on patient characteristics and preferences. The recommendation should therefore not lead to a change in practice. We have edited the sentence and now refer to the risks and benefits of the procedure and have deleted the reference to the specific examples.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2020;35(9):2307-23). It is not clear which data NICE is using to reference this, as this is not reflective of current practice or contemporary data, either in the UK or internationally. A cost analysis in the NHS between minimally invasive and conventional cardiac surgery has also shown equivalent cost (Perin G et al Ann Thorac Surg 2021). We believe that minimally invasive surgery should be offered to all patients fitting the criteria we have outlined in the flow chart above, with an explanation of the benefits (less pain, shorter hospital stays, superior patient-reported outcomes, faster recovery, fewer infections), risks and alternatives. It should be performed by appropriately experienced high-volume surgeons specialising in these procedures with demonstrated high repair rates with a low incidence of recurrence of >2+ MR.	
British Association of Cardiologists of Indian Origin	Guideline	004	007-013	In our opinion this is a good recommendation, guiding the clinician as to when to request an echocardiogram	Thank you for your comment
British Association of	Guideline	004	004-006	In our opinion this is a good recommendation as it does not mandate the clinician to undertake an echocardiogram in every patient with a suspected murmur, leaving room for clinical judgement.	Thank you for your comment

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Cardiologists of Indian Origin					
British Association of Cardiologists of Indian Origin	Guideline	005	001-009	Excellent recommendation - selects the patient who needs an echocardiogram urgently	Thank you for your comment
British Association of Cardiologists of Indian Origin	Guideline	005	017-019	This is a good recommendation as: - it avoids undertaking unnecessary serial echoes in patients with mild valvular disease (except when necessary) and should help to decrease patient anxiety about mild valvular heart disease	Thank you for your comment. In response to stakeholder comments the committee have made a new recommendation to monitor people with mild to moderate valve disease every 3-5 yrs (1.4.2). This monitoring would not necessarily include an echocardiogram depending on individual patient factors.
British Association of Cardiologists of	Guideline	005 - 006	020-021 and 001-004	This is a good recommendation as it is asking clinicians to focus predominantly on moderate/severe valve disease	Thank you for your comment

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Indian Origin					
British Association of Cardiologists of Indian Origin	Guideline	006	005-019	These recommendations do not read well. Consider reorganising with simpler recommendations before more complex ones e.g,1.1.10 before 1.1.9	Thank you for your comment. The committee considered your suggestion but 1.1.8 refers to the majority of people who wish to become pregnant and therefore this is best placed first before the recommendations on people requiring expertise.
British Association of Cardiologists of Indian Origin	Guideline	007	001-008	Good recommendations on pharmacological management of heart valve disease	Thank you for your comment.
British Association of Cardiologists of Indian Origin	Guideline	011	002-020	Decisions about intervention should be made after discussion by a multidisciplinary team as recommended by the Getting it Right the First Time (GRIFT) – an NHS Improvement Programme. Using this approach will ensure that the 'right decision is made for the right patient'. Such teams are now embedded in every cardiology department across the length and breadth of the country. Referrals for valve intervention should be made to such teams and it should not simply state "not for surgery ". The guideline does not make any mention of such teams and we would request the guideline development group to re-evaluate this recommendation.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					MDTs as an example of how this may be provided.
British Association of Cardiologists of Indian Origin	Guideline	012	001-012	- The recommendations on intervention on the aortic valve are strongly in favour of surgery versus TAVI. We feel that contemporary evidence that is available in favour of TAVI (length of ITU and hospital stay, durability of TAVI valves) has not been taken into consideration before this recommendation was made. In-hospital stay used is out of date at >10 years old (PARTNER recruited 2007-2009). At that time 2 days ITU and 6 days stay was representative. In contrast FAST TAVI involving UK centres in 2017 shows mean 2 days LOS with 4 hours average in ITU. Valve durability is now published for up to 8 years (NOTION 8). - The cost effectiveness model considered in this draft guideline has used the most expensive valve technology in the NHS single cost model and older RCT's. We feel that it would be appropriate to recalculate the cost effectiveness using the latest UK TAVI registry data. - TAVI and SAVR are complementary therapies for the treatment of a prognostically important condition i.e., severe aortic stenosis. The current COVID pandemic has demonstrated the complimentary value of both treatment modalities in keeping on top of demand when ITU facilities have been stretched/scarce and staff redeployed elsewhere. There is also no mention of the legal aspects of the 'Montgomery principle'- the patient's right to choose. This is relevant as equipoise appears to have been reached between the two modalities (TAVI and SAVR) in terms of safety, efficacy and durability in the high-risk cohort of patients.	Thank you for your comment. The model was revised to use contemporary evidence instead of historical trials. In particular, ICU and LOS are now informed by the recent UK TAVI trials showing no need of ICU after TAVI. The base case scenario cost of the valve was also edited to reflect the average price the NHS is purchasing TAVI valves (source: NHS Supply Chain). The revised cost of a TAVI procedure is now around £5,500 which compares well with the figures provided by several Trusts during the consultation. Although TAVI and SAVR are complementary therapies with TAVI showing indeed promising benefits on several aspects (e.g. recovery) the price differential of the two remains still relevant. Patient choice cannot justify the use of a non-cost-effective procedure, as allocating NHS funding to a particular technology, means that

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We would request the guideline development group to re-evaluate this more recent evidence regarding TAVI before final recommendations are made	patients in other areas would have to be denied effective treatments.
British Association of Cardiologists of Indian Origin	Guideline	General		Consider signposting this guideline to NICE infective endocarditis guidelines also. Clinical guideline [CG64] Published date: 17 March 2008 Last updated: 08 July 2016	Thank you for your comment. The committee could not identify any recommendations which could link to this guideline. However, the infective carditis guideline was in the scope under related guidance and the online patient pathway for cardiac disease will signpost to this guideline.
British Association of Cardiologists of Indian Origin	Guideline	General		The COVID 19 pandemic has proved the most challenging for two areas of the guideline: - The performance of echocardiograms for diagnosis and surveillance of heart valve disorders. This is an investigation which involves close contact between the healthcare professional doing the echo and the patient and so cannot be undertaken, unless it is a dire emergency, with social distancing measures in place The pandemic has also highlighted the adverse impact of lack of ICU facilities and personnel on cardiac surgical activity for treatment of mitral regurgitation and aortic stenosis.	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
British Cardiov	Committee	General	General	We were very surprised that ***there was no patient representation (ie. a person who has personal experience of heart valve disease) on the***	Thank you for your comment. There were two lay members on the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ascular Intervention Society	membership list			***committee that drew up these guidelines***, particularly as NICE prides itself on appropriate committee structure (as recently published in HEART). The draft guideline gives no consideration to patient experience and patient preference. The comparison of surgery and TAVI is not the same as the comparison of different medication regimes. TAVI is performed under local anaesthetic, has a median hospital stay of 2-3 days and immediate recovery. Surgery is highly invasive, involving thoracotomy, general anaesthetic, more post-operative pain, intensive care stay, median stay of 8 days in total, and recovery period of 3-6 months, especially in older patients. TAVI is therefore a far preferable experience for patients. The guidelines do not appear to give any consideration to post-operative pain, duration of disability during convalescence, patient experience or patient preference.	guideline committee. All committee members had equal status. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). The outcomes you cite were captured in the review protocol which can be found in Appendix A evidence review H. The clinical and health economic evidence review and health economic model took into account quality of life following intervention and captured relevant costs to the NHS (see the committee's discussion of the evidence in evidence review H). In the economic model, people undergoing surgery are associated with a lower quality of life and higher medical expenditure during the first year to reflect the slower recovery of this procedure. We have changed the recommendations on TAVI and it is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	016	General	***Costs are influenced by ICU stay***. The NICE model used 2 days ITU stay for intermediate risk and 3 days for high risk for TAVI. Intermediate risk data are from PARTNER 2, which is a trial done in the US recruiting more than 5 years ago. The high risk ICU and overall bed stays come from PARTNER 1B, which is more than 10 years old! In the UK no patients go to ICU routinely. In the UK TAVI trial the median number of days on ICU was 0 for TAVI. The estimated length of stay in ITU for TAVI has no resemblance to contemporary practice.	Thank you for your comment. The model is now using data from the UK TAVI trial suggesting 0 days of ICU for TAVI patients at low surgical risk in the UK. ICU and hospital LOS in higher risk groups were calculated using the estimates of hospital resource predictors by Reinhoul (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/)

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervent	Economic model	016	General	***Costs are influenced by total length of stay (LoS)***. The model uses a LoS of 6 - 8 days for TAVI in Intermediate and high risk respectively vs 9 and 11 days for surgery. This is very far from current practice for TAVI. Hospital stay was much lower in PARTNER 3 and Evolut Low Risk. The	Thank you for your comment. The model is now using data from the UK TAVI trial suggesting 0 days of

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ion Society	report - TAVI			UK TAVI trial data show median LOS 3 days for TAVI vs 8 days for SAVR. The UK TAVI registry data (NICOR) show median LOS 2 days for TAVI in 2018-19. The economic model significantly over-estimates length of stay for TAVI.	ICU for TAVI patients at low surgical risk in the UK. ICU and hospital LOS in higher risk groups were calculated using the estimates of hospital resource predictors by Reinhoul (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/) Treatment effects are calculated using data from recent studies including PARTNER 3 and Evolut. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	021	016	***The relative re-intervention rate for TAVI and surgery is flawed and has a significant effect on costs.*** TAVI has evolved over the last 10 years and some older valves with a higher incidence of paravalvular regurgitation (PVL) are no longer used (eg old SAPIEN XT valve) whereas the outcomes for the current SAPIEN 3 valve have been shown to be substantially better in the UK TAVI registry. In the economic model it is therefore inappropriate to use reintervention rates for regurgitation from old devices which are no longer used.	Thank you for your comment. The evidence used for relative re-intervention rates (Ler 2020) has now been taken out of the model as the focus of the model has shifted to new generation valves. The reintervention relative effect is now based on the trials included in the literature review. The base case scenario of the model uses relative treatment effects from trials evaluating only second and third generation devices and, therefore, old generation devices with a high rate of PVL and reinterventions are not considered anymore. In addition, a sensitivity analysis where the relative treatment effect for

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					reintervention is informed by the two trials on 3rd generation devices (Sapien 3 and Evolut) was also conducted. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***The principal problem with the Economic model is that is constructed using data drawn from old trials of TAVI versus surgery***, which are not reflective of current clinical practice, and hence costs, as well as outcomes and their associated costs, are grossly inaccurate, leading to inaccurate assessment of cost-effectiveness	Thank you for your comment. We added the most recent studies (Leon 2021 and Popma 2019) to the clinical meta-analysis used to inform the model. Costs now are estimated using only UK sources (UK TAVI trial) giving a

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					cost for the procedure in line with the one reported from several trusts. In addition, treatment effects in the base case scenario are now estimated using trials on 2nd and 3rd generation valves only (PARTNER 2, PARTNER 3 and Evolut) to account for technologically improvement of TAVI valves. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***Valve cost is stated as £20,280 which is not the actual average cost paid by NHS***. The main analysis should be with the actual average cost paid. Sensitivity analyses should go below £15,000 as some valves are available via NHS commissioning for less than this now. The quoted valve cost of £20,280 for TAVI is a substantial over-estimate of the actual cost paid by the NHS.	Thank you for your comment. Following further committee discussion, the base case scenario was changed to reflect the actual mean cost incurred by the NHS to purchase TAVI valves: £17,500. This information comes directly from the NHS Supply Chain. Currently, 20% of the valves are purchased outside this scheme, but we do not know the price used for those, so we were not able to make any assumption. Moreover, a threshold analysis on the price of the valve was conducted to estimate the price that makes TAVI cost effective for each surgical risk group. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***The data from the 'low risk' trials (Evolut Low Risk, PARTNER 3, UK TAVI) is not included***, even though these trials are most recent, and far more closely reflect current clinical practice. BCIS would recommend that a data from more recent, low risk clinical trials (Evolut low risk, Partner3) should be included to reflect current clinical practice	Thank you for your comment. Leon 2021 (PARTNER 3) and Popma 2019 (Evolut) were included in the meta-analysis used to inform the treatment effects in the model. UK TAVI is still not published so the committee decided only to use it only for length of hospital stay and ICU stay. Treatment effects in the base case scenario are now estimated using trials on 2nd and 3rd generation valves only (PARTNER 2, PARTNER 3 and Evolut) to account for technologically improvement of TAVI valves. We have revised the economic model based on stakeholder comments and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***Readily available UK-specific data on outcomes and costs of TAVI in the UK from the UK TAVI database have not been used***, although they are available in the public domain. The UK TAVI database provides contemporary data on costs and outcomes and we would recommend this is considered by NICE. This is not an Industry-sponsored trial.	Thank you for your comment. Baseline risks in the model have now been revised to reflect the most recent NICOR audit on TAVI and, therefore, current UK clinical practice. The cost estimation was revised to be based on UK sources only (UK TAVI trial) and the new estimates without the valve are now in line with the figures provided by many trusts during the consultation:

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***The economic model should utilise weighting of the trial data, so that the data from the more recent trials have greater weight since they more closely reflect UK data***. TAVI is a relatively new technology which has evolved significantly in the last decade. For this reason, more recent trials of contemporary practice should be weighted to improve the accuracy of the economic model.	Thank you for your comment. The committee acknowledged that using data from all the trials would have given too much weight to trials using old generation valves. Hence, treatment effects in the base case scenario are now estimated using trials on 2nd and 3rd generation valves only (PARTNER 2, PARTNER

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					3 and Evolut) to account for technologically improvement of TAVI valves. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***Analysis of events: Stroke***. The model used by NICE suggests that strokes are higher with TAVI. In fact, contemporary studies show lower stroke rate with TAVI (PARTNER 3, Evolut Low Risk).	Thank you for your comment. Data coming from recent studies (PARTNER 3 and Evolut) were added to the meta-analysis informing the treatment effects used in the model. Treatment effects in the base case scenario are now estimated using trials on 2nd and 3rd generation valves only (PARTNER 2, PARTNER 3 and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Evolut) to account for technologically improvement of TAVI valves. The resulting treatment effect now indicates that TAVI has a lower stroke rate than SAVR and the model was edited accordingly. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Economic model report - TAVI	General	General	***Analysis of events: Hospitalisation***. The data in the NICE model seems to suggest that hospitalisations far higher with TAVI. By contrast, contemporary trials (Evolut Low Risk, PARTNER 3) show far fewer hospitalisations with TAVI. The increased re-hospitalisation rates with TAVI in the economic model are taken from outdated studies and are inconsistent with the findings of more contemporary clinical trials	Thank you for your comment. Data coming from recent studies (PARTNER 3 and Evolut) were added to the meta-analysis informing the treatment effects used in the model.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Treatment effects in the base case scenario are now estimated using only trials on 2nd and 3rd generation valves only (PARTNER 2, PARTNER 3 and Evolut) to account for technologically improvement of TAVI valves. Likewise, hospitalisation uses the same meta-analysis on second and third generation valves. The studies suggest a higher hospitalisation with SAVR in the first year, but lower for the years beyond the first one. Therefore, the model applies 2 different baseline transition probabilities and 2 different hazard ratios. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Evidence Review H	009	003	***The Evidence review should have considered trial data on trans-femoral and non-femoral TAVI separately***. The earlier trials included a significant proportion of patients undergoing non-femoral access. The data from these trials clearly showed worse outcomes with non-femoral TAVI. In contemporary practice in the NHS, trans-apical and trans-aortic/direct aortic access are rarely used, since 96% of TAVI is trans-femoral. The evidence review should therefore concentrate on the transfemoral data which reflects contemporary practice both in the UK and internationally.	The STACCATO transapical trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has now been excluded from the economic modelling based on the transapical access route not being in line with current practice. The committee agrees that the proportion of transapical in these studies procedures are higher than in current UK practice. However, in line with the review protocol, the PARTNER trial data have been included as a combined data for transfemoral and transapical TAVI. Similarly, the CoreValve high risk and SURTAVI trial data cannot be excluded from the analysis post-hoc. Additionally, it would be inappropriate

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					to exclude the CoreValve study as it is one of only few trials in the high risk cohort. TAVI route of access was included as a subgroup analysis to explore it heterogeneity was found, and not as a stratification factor in the clinical review. There were not large differences in effect estimate between the overall analysis and the transfemoral subgroup analysis. As the recommendation was driven by the cost effectiveness evidence no changes have been made to the clinical review regarding the route of access as this would not affect the conclusions of the committee. In the revised version of the health economic model, only recent trials on 2nd and 3rd generations valves were used to estimate relative treatment effects. Those are prevalently on transfemoral approach. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Evidence Review H	009	003	***Older trials included in this analysis are very different from current practice*** in a number of ways, including: • Old TAVI valve device types which are no longer used had worse outcomes in particular in relation to paravalvar leak (PVL); • TAVI was previously performed under general anaesthesia rather than local anaesthesia. • Trans-femoral access was often surgical cut-down, whereas it is now almost 100% percutaneous – no cutting or stitching is needed for contemporary TAVI.	Thank you for your comment. The STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has now been excluded from the economic modelling based on the transapical access route not being in line with current practice. In the revised version of the health economic model, treatment effects are now derived from trials using only 2nd and 3rd generations devices, which

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Trans-femoral TAVI patients (ie 96% of this population) do not use ICU beds at all. Indeed in most centres patients go to a Level 1 bed, without using Level 2 or Level 3 beds. • Hospital stay is now much shorter: the median hospital stay for TF TAVI is 2 days • In-hospital adverse outcomes are now far better, including death (1.3%), stroke (2.1%), bleeding & vascular complications (2.3%), paravalvular leak, and pacemaker implantation (7-14%) - percentage figures are from NICOR 2019-2020 audit available on the BCIS website ***The STACCATO trial should not have been included***. It includes very old data, with 100% of patients having trans-apical access for TAVI. It is no longer relevant to current practice.	should reflect contemporary outcomes and UK practice. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Evidence Review H	009	003	***The Evidence review should have included data from the UK-TAVI trial***, an NIHR-funded trial completely free of any Industry bias. Although the trial has not been published, the data are available in the public domain (presented at ACC conference March 2020).	Thank you for your comment. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow-up at present, and we have sufficient

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					published data with longer-term follow-up.
British Cardiovascular Intervention Society	Evidence Review H	009	003	The Evidence review includes some previous meta-analyses, but has excluded published meta-analyses of the trials of TAVI vs SAVR for Low surgical risk patients. These published meta-analyses all show superior 1-year outcomes for TAVI (See Siontis et al, Eur Heart J 2019;40:3143-53). The reasons for this selective approach to literature review by the NICE committee is not clear.	Thank you for your comment. No previous meta-analyses were included directly in this clinical review. Available systematic reviews and meta-analyses, including Siontis et al 2019, were assessed but provided insufficient information to be included and so were used for reference checking only.
British Cardiovascular Intervention Society	Evidence Review H	009	003	The Evidence review describes (Page 36, Line 10) "possible harm for TAVI for mortality, need for re-intervention, and hospitalisation". This statement is not consistent with the evidence. Firstly, all previously published meta-analyses have shown reduced 1-year mortality for TAVI vs SAVR (*Siontis et al, Eur Heart J 2019;40:3143-53)*. Secondly, the Committee's own meta-analysis in the Economic model shows a very strong trend for reduced 12-month mortality, even though it has excluded data from Evolut Low-risk and UK-TAVI. The evidence review which states 'possible harm for TAVI for mortality, need for re-intervention and hospitalisation' does not stand up to scrutiny.	Thank you for your comment. We have reviewed the meta-analysis that was cited and noted that it differs from the meta-analysis in evidence review H as it includes data up to 2 years, while evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes). We note also that the risk ratios or hazard ratios did not suggest large differences between the two groups for these outcomes but the committee considered any difference in mortality based on the absolute risk difference to be important. This is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for most outcomes and the role health economic modelling had in the decision process. The health economics analysis took a different approach as we sought to capture short-term mortality benefits as well to assess cost-effectiveness. Hence, we looked at mortality benefits at 1 and 2 years and assumed no benefit in the long-term, as found in the clinical review.
British Cardiovascular Intervent	Evidence Review H	009	003	With regard to hospitalisation, both PARTNER 3 and Evolut Low Risk showed substantially and significantly reduced hospitalisation at 12 months for TAVI. The Committee's Evidence review does not recognise this because ***it has not included the Evolut Low risk data***, and because it has given equal weight to much older trials which do not reflect	Thank you for your comment. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ion Society				contemporary practice. The Evolut Low risk trial publication includes the incidence of re-hospitalisation for heart failure at 12 months, which is 6.5% for surgery vs 3.2% for TAVI. This contemporary trial reports re-hospitalisation for heart failure at 12 months at 6.5% after surgery but 3.2% after TAVI.	evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Evidence Review H	009	003	***The Evidence presented on need for re-intervention with TAVI compared to SAVR is highly flawed.*** Firstly, the data come from 1 trial only (PARTNER 2). Secondly, the TAVI valve used in this trial (SAPIEN XT) is no longer available, having been superseded by a newer iteration (SAPIEN 3 / SAPIEN 3 Ultra), which has far better procedural outcomes, particularly with respect to PVL. Thirdly, re-intervention after TAVI is driven primarily by PVL. Since PVL is much less with contemporary valves, re-	Thank you for your comment. Data on the need for re-intervention outcome was available from 6 further trials in addition to PARTNER 2, but these were analysed separately because only PARTNER2 reported this as a time-to-event outcome. All data were

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intervention is also much less. Basing the evidence for the relative risk of re-intervention on 1 study of an outdated TAVI valve is therefore inappropriate. **In the UK TAVI trial, the rate of re-intervention at 12 months was 2.2% for TAVI versus 2.9% for SAVR.** These data are UK-based, far more contemporary, and would have been much more appropriately used than the PARTNER 2 data.	considered when the committee discussed the evidence. In the revised version of the model, reintervention risk ratio is calculated using studies on 2nd and 3rd generation valves. A scenario analysis where this figure is calculated from the Evolut and PARTNER 3 only was conducted as well. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow at present, and we have sufficient published data with longer-term follow-up. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervention Society	Evidence Review H	009	003	***The Evolut Low risk trial data (NEJM 2019;380:1706-1715) have been included sparingly***. Firstly, the trial has been treated separately from the other RCTs, for reasons that are unclear. Secondly, data on hospitalisation are not included, even though they have been published. Thirdly, data on 12-month mortality have not been included, even though they have been published. Fourthly, data on hospital stay have not been included, even thought they were reported in the original trial presentation.	Thank you for your comment. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. We have checked the outcome data and can confirm that hospitalisation for heart failure has been included under 'onset or exacerbation of heart failure' outcome rather than hospitalisation. The 12-month

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					mortality data are not included as there is data for 24 months and the protocol specified that we will use longest follow-up available. Regarding hospital length of stay data, we were unable to find this reported in any peer-reviewed source and so cannot include it within the analysis. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Intervent	Evidence Review H	009	008	The Evidence Review for TAVI and surgical aortic valve replacement (SAVR) includes 8 randomised controlled trials which compared TAVI and SAVR. The Evidence Review has very significant flaws as follows:-	Thank you for your comment. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ion Society				***The Review gives equal weighting to older trials which are not reflective of current clinical practice with respect to TAVI***. Since TAVI was a completely new treatment when the included trials began with STACCATO and PARTNER 1A, it is inevitably the case that TAVI has changed and evolved dramatically, both in terms of how the procedure is done, and in terms of outcomes, over the 10 year time period between the early trials, the most recent trials, and contemporary clinical practice. In contrast, SAVR was already a mature treatment, and has changed far less in terms of the procedure and its outcomes. The UK TAVI trial is a relatively recent trial carried out entirely within the NHS, which has been presented at a major international conference (American College of Cardiology, 2020) but has not been included in the evidence review. The Evidence Review should have given greater weight to the more recent / contemporary trials, specifically UK-TAVI, PARTNER 3 and Evolut Low Risk, because these reflect more closely contemporary clinical practice (especially bed occupancy) and therefore cost	evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. However, in the revised version of the health economic analysis, only recent trials on new generation valves are included, so a weighting was not necessary. However, although the STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has now been excluded from the economic modelling based on the transapical

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					access route not being in line with current practice. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow at present, and we have sufficient published data with longer-term follow-up. In the revised version of the model, reintervention risk ratio is calculated using recent studies on 2nd and 3rd generation valves. A scenario analysis where this figure is calculated from the Evolut and PARTNER 3 only was conducted as well.
British Cardiovascular Intervent	Guideline	012	003-005	***The Recommendation is in contradiction to international guidelines.*** The proposed guidance is inconsistent with established international guidelines in this area.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ion Society				The 2017 European Society of Cardiology & European Association of Cardiothoracic Surgery guidelines *(Eur Heart J 2017;38:2739-2791)* give TAVI a Class 1 indication for patients at high and intermediate surgical risk "with TAVI favoured in elderly patients suitable for trans-femoral access". These Guidelines were produced before the publication of the 'low-risk' trials (PARTNER 3 and Evolut low risk) and are due to be updated later in 2021. The 2020 American College of Cardiology / American Heart Association guidelines *(Circulation 2021;143:e72-e227)* give a Class 1 indication for TAVI, specifically recommending that trans-femoral TAVI is *preferred* to surgery in patients aged over 80, or in those younger with a life-expectancy of 10 years or less. These guidelines state that in patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery should be recommended based on shared decision-making. The current draft NICE guidance contradicts these specialist clinical guidelines and would commit patient pathways that are currently mediated by sophisticated MDT processes in the UK to a step backwards in time of around 10 years.	TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
British Cardiovascular Intervention Society	Guideline	012	003 - 005	***The NICE recommendation does not include appropriate reference to the role of the multi-disciplinary Heart team.*** *Nor does the concept of patient/family choice or* shared decision-making feature in this draft, which is directly contradicting NHSE & GMC policy. *Specifically,* this is one of the only documents in recent years reviewing treatment options in Cardiovascular Intervention and Surgery which does not mention the multidisciplinary Heart Team. Optimum clinical practice, international guidelines, and national guidelines focus on the role of the Heart Team in determining optimal treatment for each patient with severe aortic stenosis. We consider the patient to be at the centre of every Heart Team. The NICE Recommendation should refer to the importance of the Heart team in deciding between TAVI and SAVR. Indeed, guidelines for optimal Heart Team function in the management of patients with valve disease are due to be published jointly by the British Cardiovascular Society, British Cardiovascular Intervention Society, Society for Cardiothoracic Surgery and British Heart Valve Society in the next few weeks.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee agreed that shared-decision making is central to any discussion regarding intervention and this has been highlighted in recommendation 1.5.1. A cross reference to the NICE guideline on shared decision making has also been added to this recommendation.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The proposed NICE guidance, which does not support multidisciplinary teams, seems to be a retrograde step.	
British Cardiovascular Intervention Society	Guideline	012	003	In contrast to international guidelines, ***the NICE recommendations do not take any account of individual patient considerations***, in particular age, life expectancy, frailty, co-morbidity, anatomical suitability for trans-femoral TAVI, and how these factors influence the best treatment options for patients. These critically important patient factors are well established in published European (2017) and American (2020) guidelines and are routinely employed in cardiothoracic centres across the UK in their Heart Team deliberations.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability,

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
British Cardiovascular Intervention Society	Guideline	028	027	***The Recommendation is inconsistent with current clinical practice.*** TAVI is currently in widespread use across the NHS in patients who are suitable for surgery, and who may be categorised as high risk, intermediate risk, and even low risk, but in whom assessment of the individual patient by the Heart Team, based on age, life-expectancy, co-morbidities, and anatomy leads to a recommendation of TAVI. In contrast to this reality, the draft NICE guideline states that "The committee agreed that TAVI is usually reserved for when surgery is not suitable. The guidelines therefore reflect current clinical practice" (P38 Line 16). This statement is inaccurate and is universally puzzling to expert clinicians who work in the field. This calls in to question the clinical experience/knowledge of the panel members who contributed to the NICE guideline committee. For at least 10 years TAVI has been used widely in patients who would have been considered operable, but high risk. For at least 5 years TAVI has been used in intermediate risk patients, and more	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recently also for low risk patients in certain circumstances. This change has been driven by trial evidence, by heart team decision-making and by patient preference. It is inexplicable that there was insufficient expert advice available to the Guidance committee to prevent this inaccuracy to make it into the draft guidance.	Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
British Cardiovascular Intervention Society	Guideline	031	015	***The Recommendation would have an enormous and highly detrimental impact on clinical practice, and an increase in (a) mortality and (b) postcode inequity***. If the proposed guidance were to be followed, there would be a huge fall in the numbers of patients having TAVI, and a huge increase in the numbers of patients having surgery. It would not be possible for surgery to deliver the increased demand, especially in the COVID and post-COVID era, and	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patients would face huge waits and many would die on the waiting list. Published registry data show that the mortality on a waiting list for aortic valve intervention is about 4% per month. The proposed guidance is likely to substantially reduce the numbers of patients being treated effectively for severe aortic stenosis. It is unlikely that surgical units would be able to deal with the thousands of patients who would be denied TAVI as a consequence of this guidance, and the survival of patients treated medically is known to be poor.	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
British Cardiovascular Intervention Society	Guideline	General	General	The Officers and Council of the British Cardiovascular Intervention Society (BCIS), the Structural Intervention and Clinical Standards Working Groups of BCIS are unanimous in their view that the latest draft NICE Guidance on the Management of Heart Valve Disease is flawed and, in several critical respects, incorrect. This is particularly the case in the guidance for **intervention in aortic stenosis**. In our opinion, this draft guidance presents a conclusion (ie that	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments to reflect contemporary

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				all patients with severe aortic stenosis should be offered surgical aortic valve replacement (sAVR) as the first line treatment) that is flawed in the following ways: (a) ***it is inconsistent with the evidence base***, and, in particular, with the extensive series of randomised trials that compare TAVI with sAVR in high risk, medium risk and low risk individuals with severe symptomatic aortic stenosis. As such it contradicts all available international practice guidelines.(see below); (b) it presents cost effectiveness analyses based upon historical data for ITU stay & duration of admission that are ***not reflective of modern TAVI treatment;*** (c) ***it will put the lives of patients with severe symptomatic aortic stenosis at risk*** by extending the time of their access to life-saving treatment; (d) ***it is inconsistent with current contemporary practice*** as determined by the current process of multi-disciplinary team meetings that discuss individual cases in detail and take into account all aspects of each, including *patient preference*, which is overlooked. We have no doubt that patients with valve disease in the UK will suffer if these guidelines are accepted and will not reap the benefits of the last 10 years of clinical advancement and innovation.	costs and outcomes of modern valves but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention. Recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. See evidence review H for a discussion of the evidence. (a) The economic model was developed using all available evidence and trials comparing TAVI with SAVR in people at high, medium

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We will set out in detail the specific reasons why we believe that the draft recommendations on intervention for aortic stenosis by TAVI or surgery are wrong.	and low risk. The effectiveness of the model is in line with previous analyses informing guidelines and HTA. Costs have to be UK-specific and were one of the main factors affecting the conclusion of the analysis (b) the meta-analysis used to inform cost-effectiveness of the model was edited to use only recent trials on 2nd or 3rd generation devices. Likewise, ITU, PVL rates and other relevant parameters are now informed by recent studies looking at modern TAVI systems. (c) No evidence suggests that the recommendation will increase waiting time for patient with severe AS. NHS mandates an 18 weeks maximum waiting time for non-urgent, consultant-led treatments and this is applied to SAVR. Currently no specific treatment time target exists for TAVI in the UK according to Valve for Life (https://openheart.bmj.com/content/openhrt/8/1/e001547.full.pdf) and data

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					show that fewer than half of TAVI centres achieve a waiting time lower than 18 weeks. Therefore, no evidence shows that a higher number of TAVI would decrease the time people need to wait to access the treatment. (d)The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The importance of shared decision-making has been emphasised in the recommendations under 'decisions about interventions, with reference to shared decision-making as part of the NICE guideline on patient experience in adult NHS services made.
British Cardiov	Guideline	General	General	***The recommendation would be of particular harm to patients in the context of COVID***.	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ascular Intervention Society				TAVI has substantial advantages over SAVR in the COVID and post-COVID era, since there is little requirement for ICU, and hospital stay is far shorter. This is reflected in the much greater fall in the numbers of SAVR cases done in 2020 than the fall seen for TAVI. Indeed, most regions adopted policies of transferring patients from SAVR waiting lists to receive a TAVI to facilitate their treatment during the COVID surge phase. The fall in SAVR activity means that the backlog of patients requiring treatment for severe AS is substantial. In 2020 there were 5600 fewer interventions for severe AS than expected and preliminary mathematical modelling suggests that the best way statistically to address this crisis is to convert all interventions for AS to TAVI (see V-KEMS Study Group report)! If the proposed guidelines were to be implemented, the proposed massive reduction in TAVI numbers and required increase in SAVR numbers would be impossible to deliver and would inevitably result in a large number of deaths on the waiting list. Even if it were theoretically possible to increase the number of sAVR procedures, the accompanying increase in ICU usage would have hugely negative implications in hospitals where ICU capacity is under enormous pressure. In contrast, TAVI allows patients to be treated quickly, with short hospital stays, and no use of ICU. The proposed guidance is therefore particularly inappropriate in the era of COVID.	We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Intervention Society Allied Health Professional Working Group	All	General	General	The British Cardiovascular Intervention Society Allied Health Professional (BCIS AHP) working group represents a broad spectrum of allied health professionals working within cardiology, including nurses, physiologists and radiographers. The group recognises the need for high quality evidence-based care and appreciates the opportunity to be able to contribute to the consultation of the clinical guidelines. The group has had input from a large number of clinical specialist nurses who work directly with patients with valve disease and have an in-depth knowledge of the clinical pathways. [redacted]	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[redacted] The wider British Cardiovascular Intervention Society Working Group has reviewed and endorsed the feedback document. Members are as follows: [redacted]	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[redacted]	
British Cardiovascular Intervention Society Allied Health Professional Working Group	Economic Model	027	012	The group would argue that the RCT data used to inform the economic model does not correlate or provide an accurate representation of current UK TAVI practice and experience. No consideration has been given to the development of TAVI in recent years, not only from a procedural perspective but also acknowledging the service change in pre and post procedural care. Many hospitals have moved towards same day admission for TAVI patients and a recent trend has shown that a cohort of patients who are suitable for same day discharge. Both of these service changes impact on length of stay. Additionally the move towards local anaesthesia with a majority of cases being transfemoral negates the need for an ITU bed. 12 sites across the UK would like to share their combined data, taken from the last 2 years and including all patients undergoing TAVI. This has shown an average length of stay of only 2.9 days, 94% of cases were transfemoral and 94% were performed under local anaesthetic. An ICU bed was needed in only 2.8% of cases. As mentioned this service development is not accounted for and therefore the group would urge NICE to consider approaching NHS trusts to obtain data which is aligned with current practice. ***References*** *Généreux, P., Demers, P. and Poulin, F. (2016) 'Same day discharge after transcatheter aortic valve replacement: Are we there yet?', Catheterization*	Thank you for your comment. After further discussion, the committee agreed to use UK data for Length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. LOS ranges from 3 to 3.3 in TAVI.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				and Cardiovascular Interventions. John Wiley and Sons Inc., 87(5), pp. 980–982. doi: 10.1002/ccd.26059. *McCalmont, G. et al. (2020) 'Impact of a nurse-led same day admission pathway on hospital length of stay for transcatheter aortic valve implantation.* https://www.magonlinelibrary.com/doi/abs/10.12968/bjca.2020.0062 *P Williams et al (2020) Daycase Transcatheter Aortic Valve Replacement: Preliminary Experience.* https://pubmed.ncbi.nlm.nih.gov/32763082/ *Rai, D. et al. (2021) 'Transcatheter aortic valve replacement same-day discharge for selected patients: a case series', European Heart Journal - Case Reports. Edited by F. Giannini et al. Oxford University Press (OUP), 5(2). doi: 10.1093/ehjcr/ytaa556.*	The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Intervention Society Allied Health Professional Working Group	Guideline	008	006 - 007	While the group agrees with the indications for intervention, section 1.3.2 states "consider referring adults with asymptomatic severe aortic stenosis for **surgery**, if they have any of the following". In order to align with previous sections, the group suggests that this should be changed to "consider referring adults with asymptomatic severe aortic stenosis for **intervention**, if they have any of the following"	Thank you for your comment. We have made the edit you suggested. We revised the economic model based on stakeholder comments. We have changed the recommendations and TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).
British Cardiovascular Intervention Society Allied Health Professional Working Group	Guideline	010	013 - 018	The group welcomes that the guidance recommended referral for specialist assessment for **ALL** pts with severe aortic stenosis as per ESC guidelines (2017) regardless of symptomatic burden. Due to the progressive nature of aortic stenosis, under-management of **asymptomatic** aortic stenosis and of **moderate** aortic stenosis may lead to worsening heart function and untimely death, the group believes that more consideration is required regarding the ongoing monitoring of patients in section 1.4 and suggests these patients are kept under regular review at 6-12 month intervals. Guidance on the following should also be included: • Identification of the individual or team who is responsible for monitoring with the acknowledgement that allied health professionals may be a good resource to use for valve surveillance clinics.	Thank you for your comment. No evidence was identified for any mild or moderate valve disease. Consensus recommendations could not be made for mild or moderate valve disease as there was considered to be more variation in practice for these populations and the recommendation for asymptomatic severe heart valve disease could not be extrapolated to cover these populations as the difference in severity means they are different in terms of the extent of follow-up required. It was therefore agreed that research

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Recommendation that educating patients is included to ensure they are able to recognise signs indicating progression of disease and be provided with written information to support any discussion. The patient is provided with a direct contact should they wish to report worsening symptoms.	recommendations would be made to cover these areas, which included asymptomatic mild or moderate valve disease. Recommendations 1.9.2 and 1.9.4 are on a point of contact for specialist advice and on information on progression which would include symptoms
British Cardiovascular Intervention Society Allied Health Professional Working Group	Guideline	011	004 - 012	The group welcomes that the guideline acknowledges the importance of involving patients in the decision making process with regards to intervention (section 1.5.1), however the proposed guideline suggests discussing "the type of access for surgery (median sternotomy or minimally invasive surgery)." This wording does not cover all treatment options which may be available to the patient and as such does not demonstrate best practice in terms of informed consent and shared decision making. As outlined in the NICE guideline on patient experience in adult NHS services (2012), patients should be given "clear, consistent, evidence-based tailored information which includes their condition and **any** treatment options" Further to this the Montgomery case in 2015 redefined the standard for informed consent. The Royal College of Surgeons of England (2018) states that "**all** reasonable treatment options, along with their implications, should be explained to the patient". The group feel this phrase is changed to "the type of access for intervention (median sternotomy, minimally invasive or transcatheter)"	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). Transcatheter has therefore been added to recommendation The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Additionally, the 2020 ACC/AAH guideline for the management of patients with valvular heart disease state "all patients with severe valvular heart disease being considered for valve intervention should be evaluated by a multidisciplinary team" (Otto et al, 2021). This recommendation is also included in the 2017 ESC guidelines for the management of valvular heart disease and in the 2017 NICE guidelines for Transcatheter aortic valve implantation for aortic stenosis (Baumgartner et al. 2017, NICE, 2017). The proposed NICE guidelines do not include such a recommendation and the group firmly advocates its inclusion, as evidence shows that the consensus view of the expert MDT improves outcome, safety and patient-centred care (NHS Improvement, 2020, Otto et al, 2021 & Nishimura et al (2019). Further, we suggest that this recommendation is sub-categorised by guidance regarding the structure and function of the MDT, as found within pre-existing guidelines and recommendations (Otto et al, 2021, MacCarthy et al, 2021, Baumargartner et al, 2017). We suggest the following: A) Recommendation that the MDT is composed of interventional cardiologists who are expert in interventional valve procedures and cardiac surgeons who are expert in valve surgery. Imaging specialists, specialist valve nurses/co-ordinators and anaesthetists (if general anaesthesia is required) should be core members of the MDT. Other experts such as heart failure consultants, geriatricians, ICU specialists and electrophysiologists could be included in discussions if any particular aspect of the patient's condition is relevant to their area of expertise (Otto et al, 2021, MacCarthy et al, 2021)	added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				B) MDT should have allocated administrative support in order to ensure quality of patient processing (MacCarthy et al, 2021) C) MDTs should take place at least weekly, with provision made for ad hoc meetings to discuss urgent cases (MacCarthy et al, 2021) D) Decisions should be reached by the MDT and local standards of practice should be adhered to with the most current guidelines and evidence used to inform decision-making. E) Patients should be involved throughout the decision-making process and informed of any MDT decision ***References*** *Baumgartner H, Falk V, Bax J, Bonis M, Hamm, C, Holm J, Lung B, Lansac E, Munoz DR, R, Sjo¨gren, Tornos Mas JP, Vahanian A, Windecker S & Zamorano JL (2017), The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Authors/Task Force Members, European Heart Journal, Volume 38, Issue 36, 21 September 2017, Pages 2739–2791* *MacCarthy P, Smith D, Muir, D, Blackman D, Buch M, Ludman P, Appleby C, Curzen N, Hildick-Smith D, Uren N, Turner M, Trivedi U & Banning A (2021), Extended Statement by the British Cardiovascular Intervention Society President Regarding Transcatheter Aortic Valve Implantation, Interventional Cardiology Review 2021;16:e03, available at https://doi.org/10.15420/icr.2021.02*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				NHS Improvement (2020), Independent Mortality Review of Cardiac Surgery at St George's University Hospitals NHS Foundation Trust, NHS England *National Institute for Health & Care Excellence (2017), Transcatheter Aortic Valve Implantation for Aortic Stenosis, available at www.nice.org.uk/guidance/ipg586* *Otto CM, Nishimura RA, Bonow RO, et al. (2021), 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.* *Patient experience in adult NHS services: improving the experience of care for people using adult NHS services. NICE clinical guideline (CG138). 2012. https://www.nice.org.uk/guidance/cg138* *The Royal College of Surgeons. Consent: Supported Decision-Making A Guide to Good Practice. 2018. London.*	
British Cardiovascular Intervention Society Allied Health	Guideline	012	003 - 007	Section 1.5.3 states "Offer surgery, if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease". The group strongly argues that the use of this statement does not take into account the following:	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Professional Working Group				• The guideline does not recognise the large cohort of patients that are **inoperable or high risk for surgery** and would therefore be directed towards a TAVI pathway from the outset. This is evidenced in the 2019 BCIS guidance which notes that TAVI has been proven to be superior to medical therapy for inoperable patients and superior to SAVR in patients who are high risk for SAVR. The recommendation that these patients are to be offered surgery in the first instance only serves to increase the patient pathway with the addition of a surgical outpatient review. This not only places increased demand on surgical clinics, it also has a likelihood of exposing patients to potentially unnecessary tests which are a requirement for surgery but would not be mandated ahead of TAVI. Examples of such tests are spirometry, arterial blood gasses, chest x-rays and in some circumstances angiography. • **A single point of access** for patients with severe aortic valve disease is recommended in the Cardiology GIRFT Programme National Speciality Report (Clarke 2021). We acknowledge this report is yet to be published. However this report recommends that referrals should be made to the relevant heart team rather than to an individual cardiologist or surgeon. This ensures that equal consideration is given to sAVR and TAVI at the referral stage and the most appropriate treatment is determined early in the pathway. If consideration of treatment options is delayed to the time of MDT a patient is already a good number of weeks down their pathway and will need cross-referral. Single point of access minimises these delays. We acknowledge that a small proportion of patients will be	We have added a cross reference to the NICE guideline on shared decision making to recommendation 1.5.1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Service delivery including a single point of access was outside of the scope of this guideline. However, the recommendations do not preclude patients being referred to a single point of access. The committee agree that shared decision making is key and this has been emphasised in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				crossed over to a different intervention from that proposed at the start of their pathway following investigations and the MDT. Current ESC and AHA guidelines recommend aortic valve intervention is performed when aortic stenosis severity is deemed severe and there is evidence of left ventricular decompensation (Baumgartner 2017, Otto 2020). Intervention needs to be prompt before irreversible myocardial ischemia occurs as this can lead to persistent symptoms and risk adverse events (Everett 2018). The single point of access for TAVI and sAVR ensures patients do not have unnecessary delays being "worked up" for an operation that they will not undergo. Single point of access minimises delays and therefore reduces the risk that that the ideal window of treatment will be missed. BCIS recently proposed guidelines for TAVI recommending an 18 week wait for treatment from referral (McCarthy 2021). This is difficult to achieve if patients are identified for TAVI late on in their pathway. Single point of referral is also supported in the recent BHVS Blueprint (2020) this is a consensus document on service delivery and is endorsed by both the British Cardiovascular Society and the Primary Care Cardiovascular Society. This consensus document highlights a number of important points around the structure and delivery of valve services and the need to change services as they	recommendations 1.5.1 and 1.9.1. We have added a cross reference to the NICE guideline on shared decision making to recommendation 1.5.1. We have now included consideration of frailty in the committee's discussion of the evidence in evidence review H and under 'suitability for TAVI' in the section 'terms used in this guideline'. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				are "fragmented with duplication and inadequate coordination". It also emphasises that elective valve patients should be referred to a "heart valve centre" and triaged by the "heart valve team" so that patients are directed to the most appropriate clinic or services. This supports the single point of access for Aortic Stenosis. The group feel that the guideline should include: All patients referred for Aortic Intervention should be referred to a single point of access. • There has been no consideration given to the importance of **frailty** and the impact this has on surgical outcomes. Frail patients incur greater risks of complications and greater costs during and post hospitalisation compared to non-frail patients. Additionally the impact on quality of life has also been found to be greater in frail patients after cardiac surgery (Sergi et al, 2015). Frailty has been proven to be a strong independent predictor of poor surgical outcomes and mortality (Sergi et al, 2015) while the Partner IIA trial (Leon et al 2016) demonstrates when compared to SAVR, TAVI resulted in shorter recovery times and a faster return to mobility with earlier discharge. The group also acknowledges that nurses managing the pathway are well equipped with expert knowledge and expertise in frailty assessment to aid decision making to inform the heart team or multidisciplinary meeting. This would ensure the most appropriate intervention is offered with a view to ensuring the best possible outcomes for patients.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• The draft guideline does not consider the importance of **patient experience and patient preference**. Due to emerging evidence highlighting the importance of patient choice and shared decision making, we strongly recommend its inclusion in these guidelines. NICE have documented that a shared decision making guideline will be in place in June of this year and this surely supports the need for this to be included in the guideline for management of valvular intervention also. The overriding theme of shared decision making requires health professionals and patients to work together, putting people at the centre of decisions about their own treatment and care. NICE outline that treatment options should be fully explored with the patient and different treatment options available to the patient are discussed. Furthermore, shared decision making is included in the NHS Constitution and is a requirement by the General Medical Council (NICE 2021, Lee 2013). The group feel that the guideline should include: "in discussion with the patient and as part of shared decision making, treatment options for valvular intervention (median sternotomy or minimally invasive surgery or TAVI) should be discussed with the patient" • The proposed guideline does not take into account that surgery may not be the optimal treatment decided by the **multidisciplinary team (MDT)**. The Independent Mortality Review of Cardiac Surgery at St George's University Hospital summarises that the overriding principle of an MDT meeting " is to ensure best practice and to	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				provide a consensus view as to which treatment strategy is superior or most appropriate to the individual patient" (NHS Improvement, 2020) This "consensus view" is brought about by thorough examination of all available data, including cardiac imaging, expert opinion on co-morbidities, frailty, quality of life, cognition and functional scores (Baumgartner et al, 2017 MacCarthy et al, 2021). The MDT evaluates the severity and aetiology of the disease, considers the risk of futility of intervention in relation to life expectancy and considers the impact comorbidities such as severe lung or renal disease may have on procedural risk. (MacCarthy et al, 2021). Further, the MDT will assess individual risk by analysing surgical risk scores and by looking at additional factors such as calcification of the aorta, liver disease and previous radiotherapy at the chest wall (MacCarthy et al, 2021, Baumgartner et al, 2017 & Otto et al, 2021). When TAVI is being considered, the MDT will consider the feasibility and suitablity of transfemoral TAVI and may then consider alternate access TAVI (MacCarthy et al 2021). In order to achieve shared-decision making and maintain patient-centred care, the patient's wishes should also be recognised as integral to the MDT (Baumgartner et al, 2017). Therefore, depending on the outcome of the MDT discussion, the optimal treatment may be surgery by median sternotomy or minimally invasive surgery, TAVI by transfemoral or alternate	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				access route, balloon aortic valvuloplasty as a bridging procedure or palliation by medical management. **Taking all of this into consideration, the group suggests that guideline 1.5.3 should be worded "Offer patient the optimal treatment as decided at the multidisciplinary team meeting whether this is surgery by median or minimally invasive surgery, TAVI by transfemoral or alternate access, balloon aortic valvuloplasty as a bridging procedure or palliation by medical management. Offer treatment in discussion with the patient and as part of a shared decision making process. All patients referred for intervention should be referred to a single point of access.** ***References*** *ATS Statement: Guidelines for the Six-Minute Walk Test. American Thoracic Society 2002.* *Baron, SJ. Arnold, SV. Wang, K et al; PARTNER 2 Investigators. Health status benefits of transcatheter vs surgical valve replacement in patients with severe aortic stenosis at intermediate surgical risks; results from the PARTNER 2 Randomized Clinical Trial. JAMA Cardiology. 2017;2 (8); 837-845* *Baumgartner H, Falk V, Bax J, Bonis M, Hamm, C, Holm J, Lung B, Lansac E, Munoz DR, R, Sjo¨gren, Tornos Mas JP, Vahanian A,*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Windecker S & Zamorano JL (2017), The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Authors/Task Force Members, European Heart Journal, Volume 38, Issue 36, 21 September 2017, Pages 2739–2791 *British Heart Valve Society (2020). [online] BHVS Blueprint. Available at: https://www.bhvs.org.uk/bhvs-blueprint/* *Clark, S & Ray, S. 2021. Cardiology, GIRFT Programme National Speciality Report, awaiting publication* *Everett R et al. Timing of intervention in aortic stenosis: a review of current and future strategies. Heart 2018;104:2067-2076* *Extended Statement by the British Cardiovascular Intervention Society President Regarding Transcatheter Aortic Valve Implantation Philip MacCarthy, Dave Smith, Douglas Muir, Daniel Blackman, Mamta Buch, Peter Ludman, Clare Appleby,7Nick Curzen, David Hildick-Smith, Neal Uren, Mark Turner, Uday Trivedi and Adrian Banning; Interventional Cardiology Review 2021;16:e03. DOI: https://doi.org/10.15420/icr.2021.02* *F Legare, MC Politi, R Drolet, S Descroches, D Stacey, H Bekker. Training health professionals in shared decision-making: An international environmental scan. Patient Education and Counselling, 88(2)(2012)pp 159-169*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Giuseppe Sergi, MD, Nicola Veronese, MD, Luigi Fontana, MD, PHD et al. Pre –frailty and Risk of Cardiovascular Disease in Elderly men and women. The Pro. V.A Study. Journal of The American College of Cardiology 2015; 65: 10 *Granacher, U. VoLLER,h. Gait speed is not magic, but is prognostically important in older patients. European Journal of Preventive Cardiology 2018; 25 (2), 209-211.* *Lauck SB et al. Factors influencing the decision of older adults to be assessed for transcatheter aortic valve implantation: An exploratory study. European Journal of Cardiovascular Nursing, 15 (7)(2016)pp 486-494* *Leon M et al (2016) Transcatheter or surgical aortic valve replacement in intermediate risk patients. New England Journal of Medicine. Vol 37, 17 (1609-1620)* *MacCarthy P, Smith D, Muir, D, Blackman D, Buch M, Ludman P, Appleby C, Curzen N, Hildick-Smith D, Uren N, Turner M, Trivedi U & Banning A (2021), Extended Statement by the British Cardiovascular Intervention Society President Regarding Transcatheter Aortic Valve Implantation, Interventional Cardiology Review 2021;16:e03, available at https://doi.org/10.15420/icr.2021.02* *https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines/shared-decision-making*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

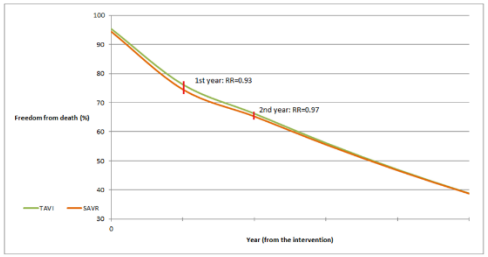
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				NHS Improvement (2020), Independent Mortality Review of Cardiac Surgery at St George's University Hospitals NHS Foundation Trust, NHS England *National Institute for Health & Care Excellence (2017), Transcatheter Aortic Valve Implantation for Aortic Stenosis, available at www.nice.org.uk/guidance/ipg586* *O E Lee, E J Emanuel. Shared decision making to improve care and reduce costs. The New England Journal of Medicine, 368 (1)(2013) pp 6-8* *Otto C M, Kumbhani KP, Alexander et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with Aortic Stenosis: A report of the American College of Cardiology Task Force on Clinical Expert Consensus documents. Journal of American Cardiology, 69 (10)(2017)pp 1313-1346* *Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021; https://doi.org/10.1016/j.jacc.2020.11.018* *Service Specification for Transcatheter Aortic Valve Implantation (TAVI). Recommendations of the British Cardiovascular Intervention Society (BCIS) – updated July 2019. Available at:*	

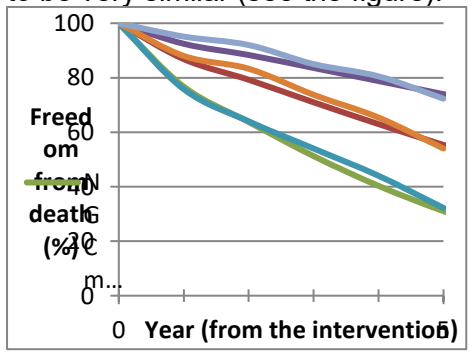
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				https://www.bcis.org.uk/resources/bcis-guidance-documents/service-specification-for-transcatheter-aortic-valve-implantation-tavi/ *The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Authors/Task Force Members: H Baumgartner. V Falk, J. Bax, M Bonis, C Hamm, J Holm, B Lung, P L, E Lansac, D R Munoz, R, Johan Sjo¨gren1, PTornos Mas, A Vahanian, T W, O W, S Windecker, JL Zamorano (2017) European Heart Journal, Volume 38, Issue 36, 21 September 2017, Pages 2739–2791*	
British Cardiovascular Intervention Society Allied Health Professional Working Group	Guideline	012	003 - 007	We suggest that up-to-date data and guidelines are factored into the analysis in determining what intervention is appropriate. The AHA/ACC 2020 (Otto et al 2020) guidelines for the management of patients with valvular heart disease were updated in December 2020. The guidelines have moved away from the risk of a patient for surgery determining the most suitable intervention to a more individualised approach. The emphasis now is on age, life expectancy and anatomical considerations of the patient. There should be equal consideration for both TAVI and sAVR for patients aged >65-80. For patients over the age of 80 with a life expectancy < 10 years and no contraindications to a Transfemoral (TF) TAVI. TF TAVI is recommended in preference to sAVR. Life expectancy is relevant with regard to valve durability. Since the first TAVI in 2007 in the UK there have been a number of generation of devices approved for use and hence long term data for the current valves in use is limited. Valve durability has however been shown to improve with new	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' includes

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				generation of devices. For example Pibarot et al (2020) was able to demonstrate that whilst the second generation of balloon-expandable valves, SAPIEN XT™, had lower midterm durability compared with SAVR, the third generation SAPIEN 3™, had better durability compared with SAPIEN XT™ and was similar to SAVR. An important factor when determining which intervention is appropriate ***References*** *Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021; https://doi.org/10.1016/j.jacc.2020.11.018* *Pibarot et al. Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. JACC 2020; 76(16):1830-43*	consideration of life expectancy under 'the benefits to quality of life (both in the short and long term) when making decisions about interventions; however, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
British Cardiovascular Society	Economic report TAVI	015		The model estimates that the mortality risk is 9% lower in the first year after TAVI, but then equal in subsequent years. This is a reasonable interpretation of the published data on longer term follow up. The BCS notes, however, that the most recent data, from PARTNER 3, showed a trend towards a much lower mortality (1% v 2.5%, a reduction of 60%) than in the model. The BCS feels that this observation should reduce the confidence of the predicted mortality difference and **sensitivity analysis should include greater reductions in mortality than 9%.**	Thank you for your comment. The meta-analysis used in the base case scenario includes the findings of PARTNER 3 study and the probabilistic sensitivity analysis takes into account the uncertainty / confidence interval around the pooled effect size.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					For longer-term mortality, the few trials with longer follow-ups (e.g. Notion), suggest that it becomes similar in SAVR and TAVI so we are allowing mortality curves to converge over time (see next graph). 
British Cardiovascular Society	Economic report TAVI	018		Survival after TAVI is compared to general population, but this is not risk-adjusted. The wider general population, especially in an under 80 group, will be in better health with better prognosis therefore than for TAVI cohort. One of the main drivers for choosing TAVI in <80 is that they have major comorbidities. It is not appropriate therefore to compare mortality after TAVI to the unadjusted general population. Conversely, mortality rates for older people undergoing cardiac surgery would be expected to be lower than the general population. This is because there is a selection process for surgery whereby people who are at high	Thank you for your comment. We recognize that not adjusting for the long-term mortality according to risk-level was at flaw of the model and this has now been addressed. The main source for relative survival, Martin 2017, was reviewed by some members of the committee and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				risk due to comorbidities are not considered suitable for surgery. In simple terms, equal age people undergoing surgery for aortic valve disease will have lower (non-valvular) risk profiles than the general population, whilst TAVI patients will generally have higher risks than the general population. It is difficult to know what the true outcomes between medical therapy and TAVI might be in mortality terms, since the only data relate to early TAVI techniques. It seems likely that the actual difference in outcomes is greater than it appeared in early trials such as PARTNER as the complication rates of TAVI have dropped markedly, as discussed, while the risks with medical therapy remain unchanged. Similar relative differences in mortality are likely to also be the case in high risk surgical cases, given the more rapid improvement in TAVI techniques than with surgical approaches. BCS acknowledge that this improvement in relative mortality in the higher risk groups will be difficult for NICE to model as there are no recent RCTs looking at the highest risk groups (nor unlikely ever to be, given the ethical problems this would pose). Nevertheless, BCS would ask NICE to consider the improving outcomes with contemporary TAVI when considering outcomes such as mortality in the higher risk populations. QALY gain with TAVI is likely to be considerably higher than it was in PARTNER, tilting the cost effectiveness comparison ever further towards TAVI.	assessed to be representing mostly TAVI patients at intermediate risk (STS 5.6 score). Therefore, the mortality calculated using Martin was assigned to the population at intermediate risk. Mortality for high and low risk people was calculated by combining the Martin 2017 data with confounder-adjusted hazard ratios from the literature (https://www.ajconline.org/article/S0002-9149(15)02009-3/fulltext). The resulting survival curves were compared to the ones of the trials with the longest follow-ups and were found to be very similar (see the figure): 

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Regarding the expected difference in mortality between TAVI vs SAVR due to the different comorbidities of patients, the model is based on randomized-controlled trials, meaning that we assume we are comparing patients who have the same characteristics (age, sex, surgical risk and comorbidities). The model is now using a risk-pooled treatment effect coming from a meta-analysis including only 2nd and 3rd generations valves. As BCIS recognized, there are not recent trials (with new generations TAVI valves) on high risk so we were unable to apply a different treatment effect to each risk group. This has been mentioned in the report as one possible limitation. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Society	Economic report TAVI	043		The BCS notes that even without adjusting the model to account for contemporary costs, QALY gains, and data, TAVI was calculated in a "most favourable" scenario to be cost effective at a level of £25,993 per QALY. Since many of the assumptions and costs used in the baseline analysis are incorrect and biased against contemporary TAVI, the BCS is confident that this "most favourable" scenario is, in fact, much more likely to be a true reflection of the cost per QALY for contemporary transfemoral TAVI procedures across the various risk categories than NICE's main conclusion from its cost-effectiveness analysis. The BCS therefore suggests that, pending a full re-analysis of the costs and outcome data as outlined above, **The 'most favourable scenario' be taken as the basis for making recommendations on TAVI use in the UK.**	Thank you for your comment. The analysis was revised using contemporary cost and effectiveness data so it should reflect the cost-effectiveness of TAVI in the UK. The conclusion is that TAVI is cost-effective for high risk people but not for intermediate and low (please see the full discussion in the economic report). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Society	Economic report TAVI	General	General	**Health economic analysis of TAVI – detailed response from the BCS** The BCS has grave concerns regarding the methodology used to assess the efficacy and cost effectiveness of TAVI compared to cardiac surgery. The key shortcoming of the analyses is failure to appreciate that TAVI is a rapidly evolving technology. The procedure and device that was called TAVI in 2010 bears little resemblance to the TAVI of today. This is crucially important to understand and use as the basis for analysis, since it means: **Real life TAVI complication rates are substantially lower than they were in 2010, as are associated hospital costs, and long term outcomes are much better (especially in terms of paravalvar leak, reintervention rates and stroke risk).** Patient feedback received by the BCS included the observation, "it is clear that treatment of valve disease is a developing field, where one would expect to see advances in procedures, better outcomes and lower costs as the weight of research brings benefits to patients and providers."	Thank you for your comment. 1. ICU and hospital LOS after TAVI are now informed by the UK TAVI trial in the low-risk scenario to reflect UK current practice: 0 ICU and 3 LOS. Baseline risks for TAVI now use the latest BCIS NICOR audit data for TAVI, which are used to calculate the related rates in the surgery arms using relative treatment effects from the trials. Treatment effects now come from a meta-analysis including only trials conducted on 3rd and 2nd generations valves only. Risk ratio vascular complication is now 1.46 (TAVI vs

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We believe that these issues have not been adequately addressedin the design of NICE's HE analysis. The BCS feels that there are three main areas which require particular consideration: **1. Improvements to the TAVI procedure which lower complication rates and costs** This is very important to populating a relevant cost-utility analysis. General anaesthesia (GA) was initially standard for TAVI implantation. Now GA is rarely required for TAVI - local anaesthesia and sedation were used in 91% of TAVI cases in 2019-20 compared with only 7% in 2010 (British Cardiovascular Intervention Society audit returns). There is a much-reduced need for an anaesthetist to be present for the procedure. The procedure was initially guided by transesophageal echocardiography (TOE), alongside x-ray guidance. TOE is no longer used routinely during the TAVI procedure. There is therefore no longer a need for a TOE operator (in the UK, typically a consultant cardiologist) for the great majority of TAVI cases. Initial practice was to arrange for a cardiac theatre team to be on standby in case of the need for urgent cardiac surgery to treat a procedural complication. This was resource-intensive, but is no longer required. Conversion to full sternotomy is now very rare (0. 45% of UK cases in 2019-20). Crossover (i.e., conversion to the other intervention modality)	SAVR) reflecting the findings of PARTNER 3. The cost of the valve in the base case scenario is £17,500 which is the average price TAVI valves are currently purchased in England and Wales(source: NHS Supply Chain). A threshold analysis has been conducted to determine the price of the valves achieving cost effectiveness in the different risk groups. This price is not far from the price TAVI valves are purchased at in other countries e.g. £14,500 in Canada (https://www.dovepress.com/a-canadian-cost-effectiveness-analysis-of-sapien-3-transcatheter-aorti-peer-reviewed-fulltext-article-CEOR), £12,000 in France (https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036577833). If TAVI was sold to the NHS at a similar price, TAVI would likely be cost effective for all risk groups.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				was 0.2% in both surgery and TAVI arms in PARTNER 3, and 0.6% with TAVI, 0.3% with SAVR in Evolut. The need for intensive care unit (ICU) stay after TAVI is now very uncommon and generally only occurs if there has been a major complication, e.g. requirement for surgery. Contemporary mean ICU is less than one day and the median stay is zero days. The assumption of a three-day mean ICU stay for high risk patients and a two-day mean ICU stay for intermediate risk patients after TAVI is completely outdated and should not be used in a cost-effectiveness assessment of modern-day TAVI. Length of overall hospital stay has fallen from the long stays seen in the early days of TAVI. The NICE model assumed a mean (and median) LOS of 8 days for TAVI in high-risk patients for surgery and 6 days for intermediate risk patients for surgery (12 days and 9 days, respectively, for SAVR). Mean LOS for elective patients in the UK in 2019-20, however, was 5.7 days with a median of 3 days. Practice is evolving rapidly and current timeframes are almost certainly shorter than this with the potential for still further reductions. One UK centre has published data indicating that a nurse-led same day admission pathway, could reduce to median LOS to 1 day, with a mean of 1.5 days (*see JACC: cardiovasc Int. 13 (15), 2020 August 10, 2020:1833–45*). Dual femoral access with 22-24 Fr catheters was required for the earliest TAVI valve implantations, whereas current versions require only single femoral access through a 14-16 Fr sheath. This together with dedicated arterial closure devices has resulted in lower rates of bleeding and vascular	2. The rate of paravalvular leak was reduced to reflect improvement of recent valves (Sapien 3). It is now 2.7% for moderate and severe PVL which is in line with the latest figure reported in the NICOR audit (Ludman 2020) Reintervention treatment effect is now calculated from a meta-analysis including the following trials: • PARTNER 2 • PARTNER 3 • Evolut This gives a risk ratio of 1.87 which is significantly lower than the odds ratio used in the consultation version of the model. We do not think that the study from Rodriguez-Gabella used to extrapolate reintervention rate in the surgical arm is over-estimating reinterventions in the UK. The latest UK study reporting aortic valve reintervention, the UK TAVI trial

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				complications. Vascular access site complications occurred in 2.3% of UK TAVI patients (2019-20 BCIS audit data). This represents real life outcomes in a large unselected cohort. The health economic model assumed a baseline risk of 3% with surgery and a relative risk of 2.45 with TAVI, but in PARTNER 3 major vascular complications occurred in 2.2% of people undergoing TAVI compared with 1.5% of people having surgery, i.e., a relative risk of vascular complications for TAVI of 1.47, not 2.45. The BCS observes that pacemaker requirement is dependent upon which TAVI device is used. Current UK pacemaker implant rates are 7% following TAVI using an Edwards valve and 15% using a Medtronic valve. The current in-hospital stroke risk following TAVI is 2.1% (2019-20 BCIS audit data) compared with 3% in 2013. The decision tree used a baseline risk estimate for stroke following SAVR of 5.4%, with a relative risk of 0.89 with TAVI. This appears to overestimate the stroke risk associated with contemporary TAVI procedures. The assumptions on bleeding risk in the NICE model are excessively high. The model assumed a baseline risk of 28% with surgery and a relative risk for TAVI (v SAVR) of 0.51. However, in PARTNER 3 (S9 table https://www.nejm.org/doi/suppl/10.1056/NEJMoa1814052/suppl_file/nejmoa1814052_appendix.pdf), life-threatening/major bleeding occurred in 3.6% of TAVI patients compared with 24.5% in SAVR patients. The relative risk for bleeding following transfemoral TAVI in contemporary practice is therefore 0.15, not 0.51. Life threatening bleeding after TAVI was 1.2% compared with 11.9% after surgery, an even greater relative risk reduction	(http://www.clinicaltrialresults.org/Slides/ACC%202020/UKTAVI_Toff.pdf), found a reintervention rate of 2.9% after SAVR compared with the 1.4% used in the model. 3. The cost-effectiveness analysis is now taking the treatment effects from trials focused on transfemoral approach: PARTNER 2, PARTNER 3 and Evolut trials. Likewise, baseline risks data come from the latest BCIS NICOR data, which reflect mostly the outcomes of the transfemoral approach, which is the most common approach used in the UK. 4 QALYs improvement due to TAVI are captured in terms of less long-term adverse events (stroke and dialysis) and a quicker and easier recovery after the intervention (people after TAVI enjoy a higher QoL than people after SAVR during the first year).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				with TAVI. UK registry data for (all) TAVI cases performed between 2019-2020 recorded major or life-threatening bleeding rates of 2.25%. The rate of major/life-threatening bleeding was 2.0% after elective transfemoral cases performed during the same time period. Much of the invasive medical equipment (e.g. urinary catheters, central venous lines, post procedural arterial lines, etc.) used during early TAVI cases is no longer required for routine cases. The health economic model uses a £20,280 price for a TAVI. This is the price quoted on the NHS supply chain website for a BS Lotus valve. No other valve was costed. This is not an appropriate cost reference to use in the model because the LOTUS valve was withdrawn from sale some years ago. Nor was it ever the main TAVI valve used in the UK. There are TAVI prostheses in common use in the UK which cost considerably less than the reference cost used by NICE. The model must use accurate contemporary costs for the commonly used TAVI valves. The BCS would welcome the availability of TAVI prostheses at lower cost to the NHS for the benefit of the whole health economy. Within the current NHS structure, it is the role of NHS procurement to negotiate valve pricing at national level with the device companies. Similar negotiations have helped UK people to benefit from new cancer drug treatments. These progressive improvements have shifted the standard of care for the delivery of TAVI (as detailed in the "Valve for life" proposed benchmark standards). They substantially reduce the cost of the procedure. It is not	We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				appropriate to use costs and risks from studies which relate to early, now obsolete, techniques and technology. The BCS suggests that **NICE updates its cost-effectiveness model using contemporary data, ideally from the UK, regarding TAVI complication rates such as major bleeding and vascular complications , ITU use, and overall length of hospital stay. Costs also need to reflect accurate current UK costs for TAVI devices. Relative risks need to be corrected to reflect contemporary, rather than historical practice.** and **NICE make explicit and publish the price differential for the device at which transfemoral TAVI becomes cost-effective using the new analysis** **2. Reduction in repeat procedures following TAVI due to near-elimination of moderate and severe paravalvar leak due to CT sizing and procedure planning and advanced TAVI engineering.** The NICE health economic model assumed paravalvar leak rates of 0.45% for SAVR and 4.6% for TAVI. This is not an accurate reflection of current TAVI technology. The rate of paravalvar leak causing moderate or more aortic regurgitation in the PARTNER 3 trial was only 0.6% in the TAVI group at one year (compared with 0.5% in surgical group, a non-significant	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				difference), as opposed to 6.8% (SAVR 1.9%) at one year in the much earlier PARTNER trial. Valve "durability" and reintervention rates are closely related to paravalvar leak rates. Two-year aortic valve reintervention rates (the most recently available published data) in the PARTNER 3 data were consequently low at 0.8% for TAVI (and 0.9% for surgery). It is not at all reasonable therefore to project from data on technology that no longer exists, a substantially higher rate of aortic valve intervention at two-year, five-year, and longer time points. Figure 6 in the NICE cost-utility document is inaccurate and misleading. It is based, quite inappropriately, on the extrapolation of results from early generation TAVI valves which are no longer used. There is no credible mechanism for why curves would diverge so dramatically at 10 years. It suggests 5-year reintervention rates around 8% for TAVI. This is not supported by evidence. In the PARTNER 2 trial (Salaun *et al)*, the 5-year reintervention rate in the TAVI group was 3.2% (compared to 0.6% in the surgery group). Importantly, not all reinterventions are associated with similar risks, implications for the patient, or use of healthcare resources. The reinterventions in the TAVI group carried a 0.6% mortality, whilst the reinterventions in the surgical group, although fewer in number, were associated with a 50% mortality rate. Notwithstanding the lower rates in the PARTNER 2 trial than indicated in the NICE health economic model, its direct relevance to current TAVI practice is now limited given substantial advances in TAVI techniques and technology.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The NICE model assumes reintervention baseline (surgery) risk at one year of 1.4% with a relative risk of 3.5 for TAVI. This is not accurate. As mentioned above, the recent PARTNER 3 trial, which used near contemporaneous TAVI techniques, showed that there were similar, low rates of reintervention at one year (0.6% in the TAVI group and 0.5% in the surgery group). In the Evolut low risk trial, reintervention rates (and relative risk for reintervention for TAVI compared with surgery) were also considerably lower than those used in the NICE cost-effectiveness analysis at 0.7% for TAVI and 0.6% for surgery. These data show that there is little, if any, difference in reintervention rates following TAVI compared with surgery. The relative risk is 1.2 at most, not 3.5. The BCS suggests that **NICE modifies its assumptions on the frequency of significant paravalvar leak and reintervention rates in line with published data regarding contemporary TAVI practice. Data which relate to earlier iterations of TAVI devices which are no longer used (or available) should not be included in the cost-effectiveness analysis.** **3. Superior outcomes for transfemoral versus non-transfemoral TAVI** Early TAVI procedures involved accessing the heart percutaneously through the femoral artery (transfemoral TAVI) or by a surgical procedure through the left ventricular apex (transapical TAVI). More recent alternative access routes include the transaortic approach and percutaneously from the inferior vena cava. It became clear after trials such as PARTNER that	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the transfemoral approach is far superior to the transapical approach in terms of complication rates. Consequently the vast majority of TAVI procedures are now performed percutaneously through the femoral artery, the alternative approaches being reserved for the minority of people who are not suitable for this approach due to peripheral artery disease. The switch to transfemoral TAVI as the default procedure is exemplified by the clinical trials. In the original PARTNER trial, 30% of people were treated through access routes other than the femoral artery, whereas in the more contemporary PARTNER 3 trial, all patients underwent transfemoral TAVI. Of crucial importance, this reflects what is actually happening in clinical practice in the UK, the latest BCIS audit data (for 2019-20) showing that >95% of UK TAVI procedures are performed transfemorally. It should also be noted that transapical TAVI is now performed only when no other options (including conventional surgery) are available. It makes no sense to mix complications rates for transapical TAVI with the lower complication rates of transfemoral TAVI when transapical TAVI is no longer in common practice. The NICE cost-effectiveness analysis does not differentiate between transfemoral TAVI and non-transfemoral TAVI. In our view this is a major flaw. By contrast, this important difference is recognised in the recently published American College of Cardiology guidelines. Clinical guidance for people who are suitable for transfemoral TAVI should be different from those for people who are unsuitable for transfemoral TAVI, as per the comment above relating to P12L6. Complication rates, length of hospital stay and costs related to non-transfemoral TAVI are not appropriate to use in any analysis of contemporary TAVI.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The BCS suggests that NICE analyses data for people undergoing <u>transfemoral</u> TAVI as the relevant comparator to surgical AVR. These major changes in TAVI technique and in TAVI practice mean that patients now benefit from fewer complications and better clinical outcomes with contemporary TAVI than the TAVI procedure of 10 years ago. This translates into higher QALYs with the current procedure. Thus the QALY advantage for contemporary TAVI over surgery is signifcantly higher than the 0.1 QALY used in NICE's cost-effectiveness analysis. The Canadian cost-effectiveness analysis (Canadian HE analysis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6677373/) estimated a 0.46 QALY advantage for TAVI, 4-5 times higher than the NICE estimate. Even this figure is likely to be an underestimate given the rapid evolution of TAVI. Consequently, the BCS suggests: **NICE updates its estimation of QALY advantage for TAVI over sAVR to account for the decreased complication rates and shorter length of stay associated with contemporary TAVI procedures.**	
British Cardiovascular Society	Economic report TAVI	General	General	Costs for the two procedures need to incorporate social care costs related to the procedure. In particular, the long recovery times, especially in the older/more comorbid populations, mean that there is a considerable care cost attached to surgery, compared to TAVI following hospital discharge. Discharge destination in PARTNER 3 was home/selfcare in 96% with TAVI, 73.1% with SAVR. **Corresponding UK costs should be calculated to reflect the real cost of a slower recovery following a more major invasive procedure.** This increased burden of care and loss of	Thank you for your comment. The cost of intermediate centre care and home-based rehabilitation is already included in the model and using the percentages provided in PARTNER 3 (Mack 2019) and the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				independence has to be reflected not only in financial terms but also in decreased quality of life for those more vulnerable people.	National Audit of Intermediate Care for costs. The burden of the loss of independence during the first months following surgery is already captured in the model as, after SAVR, two different utility scores are applied in the first and the second year with the first being lower to account for the months lived in worse health.
British Cardiovascular Society	Guideline	004	008	The phrase in parentheses does not seem necessary and could be deleted.	Thank you for your comment. The committee considered that these examples would help the referring health professional
British Cardiovascular Society	Guideline	005	004	P5 line 4 and elsewhere. The BCS supports the establishment of valve clinics, as described in the British Heart valve Society document "Network based care for heart valve disease, April 2020". The BCS suggests in 1.1.3 the phrase **"specialist assessment, ideally in a dedicated heart valve clinic"** in place of "specialist assessment". Same applies to recommendation 1.1.9.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.
British Cardiov	Guideline	005	004	Syncope is, elsewhere in NICE guidance, an indication for review within 2 weeks. Exertional syncope with a murmur is equally urgent.	Thank you for your comment. Recommendation 1.1.3 has been

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ascular Society				The BCS suggests changing 1.1.3 from four weeks to **two weeks** accordingly.	changed and now refers to within two weeks
British Cardiovascular Society	Guideline	005	017	1.1.6 and 1.1.7 would make more sense if their **order was reversed**. It should be made clear in 1.1.6 that it refers to patients with mild disease, other than the special circumstances outlined in 1.1.7, i.e. bicuspid valve disease or MVP	Thank you for your comment. We have reordered the recommendations as suggested.
British Cardiovascular Society	Guideline	005	020	1.1.7 The BCS notes that this recommendation only applies to moderate or severe valve disease. The BCS feels that there is a risk of inaction for patients who may develop significant valve dysfunction while still suitable for intervention. For example, a person aged 65 with mild calcific aortic stenosis or mild MS with rheumatic appearance.	Thank you for your comment. The committee have made a new recommendation to monitor people with mild to moderate valve disease every 3-5 yrs (1.4.2).
British Cardiovascular Society	Guideline	006	007	It is unclear why these recommendations are for cardiologists only. Would obstetricians, general practitioners and others involved in the care of such patients not also find the recommendations valuable? The BCS suggests **deleting this line** as of no value.	Thank you for your comment. We have deleted the line
British Cardiovascular Society	Guideline	006	013	The establishment of specialist heart valve clinics (as noted above) would also mean that women in these situations could be looked after in those clinics. The BCS suggests changing the wording in 1.1.10 to **"to a heart valve clinic or a cardiologist with expertise in the care of pregnant women"**	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.
British Cardiov	Guideline	007	003	It is unclear why this recommendation is in a heart valve disease guideline at all. It would be made more clear if it said "No clear evidence was found to support the use of statins in heart valve disease. Statins should be used	Thank you for your comment. We have removed the recommendation

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ascular Society				in line with the recommendations in the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification." Alternatively, this recommendation 1.2.1 could be **removed entirely** as it currently has no relevance to heart valve disease.	
British Cardiovascular Society	Guideline	007	007	It would seem appropriate to mention other treatments for heart failure in valve patients when they have concomitant left ventricular dysfunction, as is commonly the case. The BCS suggests adding a recommendation **"When adults with heart valve conditions and heart failure also have left ventricular dysfunction, refer to NICE guideline on chronic heart failure in adults. Be aware that acute heart failure due to valve dysfunction may be treated with interventional procedures or surgery"**	Thank you for your comment. We now refer to the NICE guideline on chronic heart failure as suggested to alert the reader to the management of this condition.
British Cardiovascular Society	Guideline	008	007	The BCS suggests that "for surgery" should be replaced by **"for intervention"** as some cases will be equally/better treated by percutaneous means. This would be consistent with recommendation 1.3.3	Thank you for your comment. We have made the edit you suggest. We revised the economic model based on stakeholder comments. We have changed the recommendations and TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Society	Guideline	008	014	The parameters defined for low flow low gradient AS are not universally agreed upon. Different research studies have used different definitions and this needs to be recognised rather than constraining readers to a single narrow set of definitions. Other parameters considered important include contractile reserve – the increase in VTI in response to dobutamine, change in AVA on stress and increase in mean gradient on stress. Furthermore, there are a significant number of patients, especially older people, with low flow/low gradients in the presence of preserved systolic function. Consideration of this group also needs to be included.	Thank you for your comment. The parameters included are the more generally agreed and commonly used parameters with more robust evidence. For example, from your comment, contractile reserve is not a parameter of AS severity and, although the term is used interchangeably, is not currently assessed. What is assessed is flow reserve and it is assumed to represent contractile reserve. Regarding paradoxical low flow/low gradient AS, no robust evidence was found to underpin a specific recommendation, however, the recommendation on use of CT calcium score when echo is not conclusive on the severity of the aortic stenosis is valid for these patients too.
British Cardiov	Guideline	008	022	CT calcium score is to assess the severity of the stenosis, rather than to assess need for intervention, although clearly there is a relationship	Thank you for your comment. We have edited recommendation 1.3.4 to reflect your comment 'Consider

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ascular Society				between these two things. This may be of particular value in the presence of impaired left ventricular function. The BCS suggests **"If the severity of symptomatic aortic stenosis is uncertain, for example in the presence of impaired LV function, consider measuring aortic valve calcium score on cardiac CT to assess the severity and any need for intervention**	measuring aortic valve calcium score on cardiac CT if the severity of symptomatic aortic stenosis is uncertain'. '
British Cardiovascular Society	Guideline	009	001	This recommendation does not seem to have any great significance. Heavily calcified valves are the norm in patients undergoing TAVI. Indeed a valve without significant calcification might be unsuitable for TAVI implant. Conversely, surgery may be relatively contraindicated if there is heavy calcification of the aorta, a so called "porcelain aorta". This recommendation needs to be clarified. The BCS feels it would be better still **just deleted**.	Thank you for your comment. Although high calcium burden indicates severe aortic stenosis, extremely high calcium burden asymmetric distribution and calcium burden in the left ventricular outflow tract increase the risk of the procedure and the likelihood of unwanted consequences like paravalvular leak. The committee agree with BCS that, indeed, high calcium burden and distribution in the entire aorta (eg porcelain aorta) should be part of the decision making. The committee did not suggest what decision the team should make in these cases, just highlighted the importance to take this into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Society	Guideline	009	004	"Offer" is a strong recommendation. Yet it is not made clear what is meant by more frequent reviews, nor what further tests should be performed in such patients and how often. This is of no help to clinicians or patients. If there is no clear evidence on these points, then it is hard to understand how it attracts an "offer" recommendation. If there is clear evidence on how regularly to follow up such patients and with which tests, these should be laid out here.	Thank you for your comment. Most of the evidence suggested that myocardial fibrosis was associated with increased risk of a poor outcome in severe aortic stenosis. This was in line with the committee's experience that myocardial fibrosis in general, not only in aortic stenosis, is associated with a worse prognosis. Furthermore, myocardial fibrosis in people with severe aortic stenosis indicates early decompensation and the possible need for early intervention to stop progression, because midwall fibrosis cannot be reversed or improved by intervention. The committee agreed that follow up should be enhanced and further assessment should be offered in those with midwall fibrosis to check for symptoms and enable earlier aortic valve intervention to improve prognosis. The evidence was not robust enough to recommend intervention based on midwall fibrosis. No evidence was available on the type and frequency on follow up and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					therefore a recommendation could not be made on this.
British Cardiovascular Society	Guideline	009	006	MRI is mentioned here and nowhere else. If MRI has a strong evidence base in the follow up of aortic stenosis patients, the BCS feels that **a separate recommendation should be made to offer/consider MRI in clearly defined populations**.	Thank you for your comment. The committee agreed not to recommend specific circumstances in which MRI should be performed as the evidence for this was not reviewed. People have MRI for variable reasons and we are just advising on how to use the result if MRI was performed and it shows mid-myocardial fibrosis. This has been clarified in the committees discussion section. The evidence was not robust enough to recommend offering MRI in severe AS, or to recommend intervention based on the finding of mid-wall fibrosis. However, the evidence was robust enough to underpin a recommendation of enhanced follow-up in patients that happened to have had an MRI that demonstrated mid-wall fibrosis.
British Cardiovascular Society	Guideline	009	009	"for surgery" should be replace by **"for intervention"** in 1.3.7 as some cases will be equally/better treated by percutaneous means. For example, aortic regurgitation in a bioprosthetic valve/paravalvar leak/AR in the presence of calcific aortic stenosis. This would be consistent with recommendation 1.3.3	Thank you for your comment. We have edited the rec to say 'intervention' as we now recommend TAVI for patients at high surgical risk.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Society	Guideline	010	001	Tricuspid regurgitation is not uncommon, either in combination with mitral regurgitation or aortic stenosis or as a separate condition. The BCS suggests that **A recommendation should be made as to what, if any, evidence there is for repair of the tricuspid valve as a standalone procedure, or in conjunction with intervention for other valve conditions.**	Thank you for your comment. Unfortunately, no evidence was found on indications for interventions for tricuspid regurgitation. The committee has now made consensus recommendations on interventions for tricuspid regurgitation (1.5.14 and 1.5.15).
British Cardiovascular Society	Guideline	011	005	The BCS feels very strongly that NICE has *not* adequately reflected good practice in decision-making around intervention in valvular heart disease. This is currently widely implemented through the use of multidisciplinary team meetings. Typically, these include (at least) an experienced cardiac surgeon, a structural interventionist and imaging specialists, with input from other clinicians who know the patient's circumstances and views well. The patient's voice should be very clear in these discussions, either directly, or through those who are looking after them. One patient's feedback to the BCS concerning this draft NICE proposal include the comment, "I think this is a worrying proposal for patients that would be opposed by groups representing the generality of patients, not just cardiac groups." The BCS suggests a new recommendation: **"Decide on timing and nature of intervention for people with valvular heart disease after discussion of the case, including the person's own views, at a properly constituted multidisciplinary team meeting"**	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee agree that shared decision making is essential when discussing intervention and this has been highlighted in recommendation 1.5.1. A cross reference to the NICE guideline on shared decision making has been added to this recommendation. NICE guidelines can only offer patient

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					choice between interventions which are cost effective.
British Cardiovascular Society	Guideline	011	007	Many people with valvular heart disease are of advanced age and the impact of cardiac surgery is considerable. The BCS feels there should be explicit discussion of the likely extended recovery time after hospital discharge for patients undergoing surgery compared with the rapid recovery from percutaneous treatment. We welcome the use of shared decision-making with patients to come to a decision about valve intervention. Patient responses to the BCS regarding this draft NICE guidance included the comment, "I would question whether the NICE data recognises the benefits of TAVI over the 'hit' from a major operation, which is survived at the cost of much reduced quality of life by comparison.". One specific difference which does not receive specific mention is the amount of pain a person is likely to experience undergoing the different valve interventions and how long they are likely to experience pain.	Thank you for your comment. Quality of life was included as an outcome in the review so data regarding the differences between TAVI and surgery for this outcome was captured. Pain was not prioritised as an outcome in the review protocol so was not included in the review. Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiov	Guideline	011	008	The issue of valve durability is a complex area. In early TAVI trials, lower valve durability (usually due to paravalvar regurgitation) was seen	Thank you for your comment. The committee acknowledged the fact that

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
ascular Society				compared to surgical replacement. However, this no longer reflects current practice as such TAVI valves are no longer available and the newer valves are specifically designed with this durability/paravalvar leak issue in mind. Available evidence (e.g., PARTNER 3) suggests there has been a major reduction in such complications. Discussions should be based on the most recent data, not on data regarding technology that is no longer used. Evaluation of the long-term durability of implanted valves is further complicated by recognition that early TAVI practice led to the implantation of undersized valves. The routine use of cardiac CT to size valves appropriately has resolved this problem and improved procedural outcomes. There are very little data on the comparative longevity of bioprosthetic valves and contemporary TAVI valves. In PARTNER 2, repeat valve intervention was primarily for aortic regurgitation, rather than for TAVI prosthesis deterioration, something that is much rediuced with later valve developments. Longevity data are available for some, but not all, surgically implanted bioprosthetic valves. Finally, the development of effective percutaneous devices to treat paravalvar leaks (in either surgical or percutaneous valves) has meant many patients can avoid repeat valve surgery, even when paravalvar regurgitation is found, extending durability.	the need for re-intervention may reduce with more contemporary valves and this was incorporated into the discussion section of the evidence review. The revised version of the model calculates treatment effects using trials on 2nd and 3rd generation valves only. In addition, the model includes a scenario analysis where reintervention treatment effect is calculated from Evolut and PARTNER 3 only, to account for the improvement of latest generation valves. In this scenario, reintervention rates in the surgical and TAVI arms are almost identical.
British Cardiovascular Society	Guideline	011	010	Whilst it is entirely reasonable to consider different *surgical* approaches, it would not be reasonable or ethical to ignore in discussions about treatment with the person a percutaneous treatment option which is equally (or more) effective for his or her condition than surgery. The BCS feels strongly that it would put cardiologists in an impossible situation if they were not able to discuss a procedure which is already commonly used in patients at high- and, to a lesser extent, intermediate-risk from surgery, which potentially both the MDMand the patient believed is the preferred intervention because	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				of the lower procedural risks, shorter length of hospital stay and quicker recover. Of course, patients are likely to raise these issues themselves given how well-established percutaneous valve procedures are in the UK. The BCS suggests replacing this statement in 1.5.1 with **"The range of options for valve intervention that they are suitable for, for example percutaneous intervention, median sternotomy or minimally invasive surgery."**	for people at intermediate or low surgical risk (1.5.3). Procedural risk, length of hospital stay and recovery (quality of life) were included in the health economic model (see evidence review H). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Society	Guideline	011	013	The BCS is strongly supportive of the concept of shared decision-making. We feel that some of the subsequent recommendations are in direct contradiction to the basic presumption that the person and the medical team that knows them best should not make an informed choice as to the treatment that is best suited to their individual needs. The guideline does put sufficient emphasis on shared decision-making, its recommendations regarding interventions for aortic valve disease making true shared decision-making impossible. When considering valve interventions, patients need to fully understand the strengths and weaknesses of all available treatments (including no treatment) before effective shared decision-making can be concluded. This must include percutaneous options as well as surgical ones or the choice has been taken away from the person and there is no true shared decision-making. The cost-effectiveness analysis used to support the draft recommendations appears to have made no attempt to explore how the allocation of one or	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				other procedure impacts upon the person's mental health and on their quality of life. The BCS notes that people in the UK are allowed, under existing NICE guidance, to choose alternative, sometimes more costly, approaches to their treatment. An example is the option for people to choose caesarean section as opposed to vaginal delivery, after a process of shared decision-making if they believe that it is their best interests. The BCS would draw attention to the latest GMC ethical guidance to doctors on consent obliging us to give patients, in a meaningful dialogue, information on all their options. The BCS feels therefore that this patient-centred decision-making should be applied in the same way to valvular heart disease. The BCS suggests changing recommendation 1.5.3 so that it does not directly contradict recommendation 1.5.1 as follows: **"Offer valve intervention as first line treatment for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease. Choice of intervention should be determined using shared decision-making, based on individual person's characteristics and preferences, after discussion in an appropriately constituted multidisciplinary meeting."**	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The health economic model included consideration of quality of life (see evidence review H).
British Cardiovascular Society	Guideline	011	016	In line with the importance of shared decision making outlined in comment for P11L13, the BCS suggests in 1.5.2: **"When intervention is agreed, base the decision on the type of intervention (percutaneous approach, median sternotomy or**	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				minimally invasive surgery) on the person's characteristics and preferences. If minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre."	and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). We have added a cross reference to the NICE guideline on shared decision making to recommendation 1.5.1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Society	Guideline	012	003	The BCS feels that this recommendation is not consistent with good clinical practice in the UK or elsewhere. As noted above, it is incompatible with recommendation 1.5.1, which emphasises the importance of shared-decision making. We also have major concerns about the accuracy and relevance to current practice of the health economic evaluation that was conducted by NICE. **Our detailed comments on this are included below** (comments 37-41), entitled "Health economic analysis of TAVI – detailed	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				response from the BCS". See also comments about 'suitable' or 'unsuitable' in P12 Line 6. Consequently, the BCS feels that this recommendation should be, as previously noted, changed as follows: **"Offer valve intervention as first line treatment for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease. Choice of intervention should be determined, using shared decision-making, based on individual person's characteristics and preferences, after discussion in an appropriately constituted multidisciplinary meeting."**	unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					they were not cost-effective within that population.
British Cardiovascular Society	Guideline	012	006	The BCS feels that the term "if surgery is unsuitable" is insufficiently clear. The BCS suggests the following, or similar wording, for this recommendation: **When a properly constituted MDM considers transfemoral TAVI to be the best option for an individual and the person has a preference for TAVI, then surgery should be considered unsuitable for that person and TAVI should be offered.** We have similar concerns with regard to bicuspid aortic valve disease. While bicuspid valve disease was an exclusion criterion in most TAVI trials, there is now extensive experience of treating bicuspid valve disease by TAVI with excellent procedural results. It is therefore clear that TAVI is a potential treatment option for patients who have severe bicuspid aortic valve disease who are selected by an appropriately constituted MDM. Furthermore, the assessment of aortic valves in the work up for TAVI commonly identifies patients who have been incorrectly labelled as having (or not having) a bicuspid valve. The BCS suggests that **Shared decisions about suitability for TAVI, including in bicuspid aortic valve disease, should be made by a properly constituted MDM, after assessment which includes a CT scan.** The BCS suggests **removing recommendation 1.5.4 entirely**, as redundant if 1.5.3 is revised as above.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated. We have now provided a more extensive definition of suitability for TAVI in the section 'terms used in this guideline'

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Society	Guideline	012	006	A more relevant consideration than bicuspid valve status in determining the most appropriate intervention for severe aortic valve disease is whether or not transfemoral access is available for TAVI, a wealth of evidence now showing better clinical outcomes and shorter lengths of hospital stay, both contributing to better cost-effectiveness, for transfemoral TAVI than other approaches such as transapical TAVI. The BCS suggests replacing 1.5.4 with: **"Consider surgery, if suitable, for adults with severe aortic stenosis when a transfemoral percutaneous approach is not available.**	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Society	Guideline	013	002	As with aortic valve disease, it is no longer appropriate for decisions on intervention to be made without discussion of all the complexities of a case at a properly constituted MDM meeting. This will have similar characteristics to that outlined for aortic valve disease. Patients' views and opinions should be represented in such discussions.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
British Cardiovascular Society	Guideline	014	003	The BCS has major reservations about the phrasing of this recommendation. It implies avoiding percutaneous repair in such patients. This would not be an appropriate messageas it is not supported by the evidence base. The BCS suggests **"1.5.13 Consider transcatheter mitral edge-to-edge repair to adults with heart failure and severe secondary mitral regurgitation, if surgery is unsuitable and the person is still symptomatic despite optimal medical therapy"**	Thank you for your comment. The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The current recommendation does not preclude mitral edge-to-edge repair being undertaken if medical management fails to control symptoms. We have added a recommendation to make this clearer (1.5.14).
British Cardiovascular Society	Guideline	015	001	There are no recommendations in this document concerning important areas relevant to the management of patients with valvular heart disease. The BCS suggests including recommendations on: Coumarins for mechanical valves INR recommendations based on valve type and position. **Do not offer DOACs for mechanical valves**	Thank you for your comment. This topic was not prioritised for inclusion in the scope as there is very little variation in clinical practice in how people with mechanical valves are managed.
British Cardiovascular Society	Guideline	015	002	The BCS feels that 1.7.1should read **"Do not offer anticoagulation after surgical biological or percutaneous valve replacement unless there are other indications for anticoagulation."**	Thank you for your comment. The committee were unable to make a 'do not' recommendation for anticoagulants following transcatheter valve implantation due to the limited evidence.
British Cardiovascular Society	Guideline	015	004	It is reasonable to consider SAPT (single antiplatelet therapy) after TAVI, but it may well not be necessary at all. The BCS suggests adding to 1.7.2 **"Be aware that there is limited experience of implanting TAVI without any antiplatelet therapy"**	Thank you for your comment. The recommendations are made when an action is required and therefore suggested text has been added to the committee's discussion of the evidence in evidence review J.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Cardiovascular Society	Guideline	015	010	Remote monitoring and phone support for people with valve disease is now commonplace and may be provided through a valve clinic. This may mean less need for regular monitoring. The BCS suggests adding to 1.8.1 as a consideration **"The availability of dedicated remote support, for example through a valve clinic service."**	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline.
British Cardiovascular Society	Guideline	017	003	The BCS suggests rephrasing 1.9.5 to highlight the value of valve clinics as follows: **"Provide information and support to young adults regarding transition from paediatric to adult services, including ongoing care in heart valve clinics"**	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite heart valve clinics as an example of how this may be provided.
British Cardiovascular Society	Guideline	038	018	The BCS strongly disagrees with the statement that offering surgery when suitable reflects current practice. The definition of "suitable" is critical here to understanding the recommendation, but the clear implication from the document is that it includes patients who are at high risk of complications following SAVR. This would be a complete change from current UK practice which, in our opinion, would be a huge retrograde step and	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				unworkable in practice. The increasing numbers of TAVI procedures performed in the UK demonstrate clearly that, as in many countries around the world, a large proportion of patients technically suitable for surgery already undergo TAVI following MDM review. The BCS notes also that TAVI is increasingly performed in the UK for people with bicuspid aortic valve disease.	unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The committee noted that most people with bicuspid aortic valve disease would need aortic valve replacement at a much younger age, making them ineligible for TAVI. The recommendation made does not preclude it being performed in those with bicuspid aortic valve disease at all, but this population was not included in the recommendation due to a lack of RCT evidence in this specific population.
British Cardiovascular Society	Guideline	043	016	The BCS disagrees that no impact on practice results from this recommendation. Transcatheter mitral valve repair is currently performed, at low levels, in the UK. Its use tends to be determined by specialist MDM discussions. However, these include people with secondary mitral regurgitation and, based on the COAPT trial, such patients are now being offered edge-to-edge repair if they meet the trial inclusion criteria.	Thank you for your comment. The recommendations were changed to allow people who show symptoms under medical management to obtain edge-to-edge repair. Considering that,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Consequently, any reduction in guideline support from NICE for such patients will lead to a change in practice (i.e., a reduction in numbers of people undergoing this procedure for this indication).	currently, people who meet trials criteria are not routinely offered the intervention and that a number of them will still receive the intervention under the new recommendation, we think there will not be an important change in practice.
British Cardiovascular Society	Guideline	General	General	Percutaneous valve treatments such as TAVI and edge-to-edge valve repair have been made possible by great technological advances. The same is true of sutureless SAVR. This is a rapidly evolving area which has increased the availability of treatment options for patients with valve disease, some of whom were previously untreatable. As the technologies have improved and experience in their use has increased, procedural outcomes have also improved. The UK has played an important part in this evolution. The BCS is concerned that an abrupt reduction in the availability of percutaneous valve procedures will hinder the UK's ability to contribute to future technology advancements. The UK may become unattractive for research and development in this area, with patients missing out on the incremental improvements in the treatment of valve disease. Indeed, a patient highlighted his own concerns to the BCS regarding the draft NICE guidance by reflecting, "it seems to me that the NICE proposal would have a seriously detrimental effect on the development of procedures for treating valve disease". The BCS is concerned that the patient's voice is not sufficiently evident in this guideline. No consideration has been given to the obvious benefits for the individual from TAVI in reduced length of hospital stay, reduced	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The importance of shared decision-making has been emphasised in the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recovery time at home, and less pain than after surgical AVR. Nor has any consideration been given to patient choice in decision-making and the impact upon patients of knowing that they could not undergo their preferred (less invasive) intervention.	recommendations under 'decisions about interventions, with reference to shared decision-making as part of the NICE guideline on patient experience in adult NHS services made. Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention, which in the case of TAVI included length of hospital stay mentioned in your comment. The other two outcomes mentioned in relation to TAVI were not considered as they were not in the list of pre-specified outcomes in our review protocol. Patient choice cannot justify the use of a non-cost-effective procedure, as allocating NHS funding to a particular technology, means that patients in other areas would have to be denied effective treatments.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We do not agree that the disutility of patients being allocated to a non-preferred procedure has been excluded from the model. The main reasons that people might prefer TAVI over SAVR are the adverse event profiles and the recovery time. Both of which have been explicitly incorporated in to the QALY calculations. The latter using quality of life data collected by the randomised trials. And the former, using disutility values from the wider literature. Similarly, the evidence for sutureless SAVR compared to alternative SAVR approaches was not covered in the review protocol meaning recommendations on this could not be made.
British Cardiovascular Society	Guideline and	General	General	**BCS conclusion on draft heart valve guidance** In conclusion, the BCS welcomes the opportunity to contribute comments regarding this draft guidance from NICE, some of which is perfectly sensible. The BCS recommends emphasising the need for clinical experts to lead the care of patients with valve disease in a process which involves	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	Economic report TAVI			specialist valve clinics, multidisciplinary team working, and shared decision-making with patients. Unfortunately, the NICE recommendations regarding the management of severe aortic valve disease, and its recommendations for TAVI in particular, fall down in three main areas: 1) they place insufficient emphasis on shared decision-making, 2) the cost-effectiveness analysis is based upon data which does not reflect modern-day TAVI practice, such as the (now rare) requirement for ITU stay, length of hospital stay, and thereby costs. The advances in TAVI technology and the benefits derived by patients from TAVI is an ongoing process so not only do the current draft guidelines need to be revised, they will also need to be reviewed in the near future to account for the expected continued improvements in outcomes following TAVI. 3) they do not reflect current clinical practice in the UK, which involves the routine use of TAVI in preference to surgical AVR for patients who are at high risk of complications from conventional surgery. • **It would be completely unfeasible to manage patients optimally, with open discussions about the treatment options, or to share the decision-making process with patients, were clinicians to follow these draft recommendations.** • **The cost-utility analysis needs to be repeated based on the most contemporary data available or, where such data are not available, more realistic estimates.**	added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The importance of shared decision-making has been emphasised in the recommendations under 'decisions about interventions, with reference to shared decision-making as part of the NICE guideline on patient experience in adult NHS services made. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments to reflect modern-day practice, cost and effectiveness but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). We are therefore unable to make a recommendation to offer

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• **The clinical recommendations need to be redrafted in a way which facilitates modern-day management of people with severe valve disease.**	surgical or TAVI based on shared decision making. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Cardiovascular Society Allied Health Professional Working Group Intervention Society	Guideline	012	006 - 007	The group believe the wording in section 1.5.4 to be misleading and suggests that patients with bicuspid valve morphology who are unsuitable for surgery should not be offered TAVI. Historically TAVI in patients with bicuspid aortic valves was deemed to be high risk with limited evidence to support its safety and efficacy. However, as TAVI centres continue to evolve and patient numbers increase, this in turn brings new research and evidence to support TAVI in this group of patients. The group suggest that the guideline could instead be worded: "Offer TAVI, if suitable, to adults with severe aortic stenosis, including bicuspid aortic stenosis in those requiring aortic valvular intervention". ***References*** *Anwaruddin S. et al. Systematic Approach Toward Transcatheter Treatment of BAV Disease: One Size Does Not Fit All. J Am Coll Cardiol. 2020 Sep 1;76(9):1031-1033.*	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Makkar RR. et al. Association Between Transcatheter Aortic Valve Replacement for Bicuspid vs Tricuspid Aortic Stenosis and Mortality or Stroke. JAMA. 2019 Jun 11;321(22):2193-2202. *Williams M. et al. The PARTNER 3 Bicuspid Registry for SAPIEN 3 TAVR in Low Surgical Risk Patients; Presented at TCT 2020; October 2020, tctconnect.com* *The PARTNER 3 Trial, low surgical risk bicuspid registry* *Tchetche D. et al. Bicuspid Aortic Valve Anatomy and Relationship With Devices: The BAVARD Multicenter Registry. Circ Cardiovasc Interv. 2019 Jan;12(1):e007107.* *Pasala TKR. et al. Transcatheter Aortic Valve Replacement for All-comers With Severe Aortic Stenosis: Could It Become a Reality?. Rev Esp Cardiol (Engl Ed). 2018;71(3):141-145.* *Halim SA. et al. Outcomes of Transcatheter Aortic Valve Replacement in Patients With Bicuspid Aortic Valve Disease: A Report From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2020 Mar 31;141(13):1071-1079* *Yoon SH. et al. Bicuspid Aortic Valve Stenosis Transcatheter Aortic Valve Replacement Registry Investigators. Bicuspid Aortic Valve Morphology and Outcomes After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020 Sep 1;76(9):1018-1030*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Geriatrics Society	All	General	General	The British Geriatric Society (Cardiovascular Section) welcomes the revision of these clinical guidelines. We appreciate the opportunity to contribute to this consultation.	Thank you for your comment.
British Geriatrics Society	Guideline	008	006 - 007	**BGS suggest to align with current clinical practice that assessment and suitability for intervention should be determined by a multidisciplinary heart team which acts in the patient's best interests.** Chambers et al (2017) stress 'a multidisciplinary approach is recommended for all types of valve disease.' The British Heart Valve Society publication Network Based Care for Heart Valve Disease (2020) stipulates 'assessment of patients with HVD considered for treatment should be undertaken by a multidisciplinary heart valve team (MDT) in a heart valve centre.'	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided
British Geriatrics Society	Guideline	011	004 - 012	**BGS believe a multidisciplinary approach should be encompassed within 'decisions about interventions.'** Holmes et al (2013) stress the critical role of a multidisciplinary team in 'enhancing the process of patient education and informed consent' Chambers et al (2017) elaborate that 'the wishes of the patient will inform the discussion of treatment options at multidisciplinary meetings. The consensus of the meeting will be communicated to the patient and if desired will	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				inform further discussion about the timing and nature of surgery. It may on occasion be appropriate to invite a patient to a discussion about his or her case.' S Conroy. Silver Book II: Quality urgent care for older people (2021) https://www.bgs.org.uk/resources/silver-book-ii-holistic-assessment-of-older-people David R. Holmes, Jeffrey B. Rich, William A. Zoghbi, Michael J. Mack, The Heart Team of Cardiovascular Care, Journal of the American College of Cardiology, Volume 61, Issue 9, 2013, Pages 903-907, ISSN 0735-1097 Chambers J, Ray S, Prendergast B, et al. Standards for heart valve surgery in a 'Heart Valve Centre of Excellence'. Open Heart. 2015;2(1):e000216. Published 2015 Jul 7. doi:10.1136/openhrt-2014-000216 John Chambers, Bernard Prendergast, Bernard Iung, Raphael Rosenhek, Jose Luis Zamorano, Luc A. Pierard, Thomas Modine, Volkmar Falk, Arie Pieter Kappetein, Phillipe Pibarot, Thoralf Sundt, Helmut Baumgartner, Jeroen. J. Bax, Patrizio Lancellotti; Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. Eur Heart J 2017; 38 (28): 2177–2182. doi: 10.1093/eurheartj/ehx370	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Geriatrics Society	Guideline	012	003 - 007	**BGS suggest suitability for surgery or TAVI should be determined by a multidisciplinary heart team considering individual patient characteristics.** The Cardiothoracic surgery GIRFT Programme National Specialty Report (2018) states 'successful outcomes depend on the skills and expertise of highly specialised multidisciplinary teams.' ESC/EACTS (2017) Guidance states 'decision making for intervention should be made by a 'Heart Team' with a particular expertise in VHD, comprising cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians and heart failure, electrophysiology or intensive care specialists. The 'Heart Team' approach is particularly advisable in the management of high-risk patients and is also important for other subsets, such as asymptomatic patients where the evaluation of valve reparability is a key component in decision making.' NICE recognises this concept in the transcatheter aortic valve implantation for aortic stenosis interventional procedures guidance (2017) stating 'patient selection should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				expert in cardiac imaging and, when appropriate, a cardiac anaesthetist and a specialist in elderly medicine. The multidisciplinary team should determine the risk level for each patient and the TAVI device most suitable for them.' NICE Multimorbidity guideline (NG56) (2016) advises delivery of tailored care that takes into account multimorbidity, with particular focus on: how the person's health conditions and their treatments interact and how this affects quality of life, the person's individual needs, preferences for treatments, health priorities, lifestyle and goals. It also highlights the need to establish treatment goals, values and priorities. Chambers et al (2017) discuss how 'there should be regular Heart Team meetings to discuss the indications for and timing of intervention.' Further stating 'assessment by relevant non-cardiac specialists (elderly care physician, pulmonologist etc.) should be available for patients with significant comorbidities' Kappetein et al (2012) confer that the 'multi-disciplinary team should convene as a group on a regular basis to review and interpret clinical data to arrive at a consensus on the optimal treatment strategy for each patient.' Furthermore Fletcher et all (2012) demonstrate wider benefits; 'an integrated team effort is essential to the best	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				care for each patient regarding individual management and will assure that evidence-based guidelines, in both treatment and secondary prevention, are implemented.' John Chambers, Bernard Prendergast, Bernard Iung, Raphael Rosenhek, Jose Luis Zamorano, Luc A. Pierard, Thomas Modine, Volkmar Falk, Arie Pieter Kappetein, Phillipe Pibarot, Thoralf Sundt, Helmut Baumgartner, Jeroen. J. Bax, Patrizio Lancellotti; Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. Eur Heart J 2017; 38 (28): 2177–2182. doi: 10.1093/eurheartj/ehx370 Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012 Oct;33(19):2403-18. doi: 10.1093/eurheartj/ehs255. PMID: 23026477. Fletcher GF, Berra K, Fletcher BJ, Gilstrap L, Wood MJ. The integrated team approach to the care of the	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patient with cardiovascular disease. Curr Probl Cardiol. 2012 Sep;37(9):369-97. doi: 10.1016/j.cpcardiol.2012.04.001. PMID: 22884247.	
British Geriatrics Society	Guideline	General	General	**The BGS recommends a multidisciplinary integrated care approach to older people with heart valve disease** We are concerned that this recommendation does not address the need for a collaborative multidisciplinary approach to the assessment and management of an older person with valve disease. There is strong evidence to suggest that patients who have a multidisciplinary assessment will have better outcomes. Optimal management of older adults with cardiac conditions involves integrating pertinent guideline recommendations with each unique patient's personal preferences using a process of shared decision-making (https://www.bgs.org.uk/resources/silver-book-ii-holistic-assessment-of-older-people). Shared decision making to generate a management plan that best fits the individualised personal goal and has the best balance of added value versus risks and burden. The older cohort of patients frequently display age-related physiological impairments, multimorbidity and geriatric syndromes such as frailty, sarcopenia, functional and cognitive impairment. Across surgical populations, frailty in particular is associated with higher rates of postoperative mortality, morbidity, functional decline and a prolonged length of hospital stay.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Targets: • Comprehensive geriatric assessment (a multi-dimensional interdisciplinary approach to determine the medical, psychological, and functional needs of older patients in order to develop a coordinated and integrated plan for treatment and long term management) • Multidisciplinary "Heart Valve Team" approach • Assess for degree of frailty (Clinical Frailty Scale, and Essential Frailty Toolset (EFT)) to predict outcome, aid decision making and individualised management plans. Frailty has consistently been shown to significantly predict mortality and postoperative outcomes. We suggest the use of a standard measure, such as the EFT, which can enhance the quality of frailty research in the TAVI patient population. • Individualised management plans • Maintain independence, reduce harm, reduce treatment burden, lengthen life • Database and regular data review for heart valve interventions in older people • Further research into heart valve disease in older people S Conroy. Silver Book II: Quality urgent care for older people (2021) https://www.bgs.org.uk/resources/silver-book-ii-holistic-assessment-of-older-people	We now refer to frailty under suitability for TAVI in the section 'terms used in this guideline'.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Ellis G, et al. "Comprehensive geriatric assessment for older adults admitted to hospital." The Cochrane database of systematic reviews vol. 9,9 CD006211. 12 Sep. 2017, doi:10.1002/14651858.CD006211.pub3 S G Parker, P McCue, K Phelps, A McCleod, S Arora, K Nockels, S Kennedy, H Roberts, S Conroy, What is Comprehensive Geriatric Assessment (CGA)? An umbrella review, Age and Ageing, Volume 47, Issue 1, January 2018, Pages 149–155, https://doi.org/10.1093/ageing/afx166 Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-495. doi:10.1503/cmaj.050051 Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. J Am Coll Cardiol 2017;70:689–700. 10.1016/j.jacc.2017.06.024 Li, Zhe et al. "Measurement and prognosis of frail patients undergoing transcatheter aortic valve implantation: a systematic review and meta-analysis." BMJ open vol. 11,3 e040459. 4 Mar. 2021, doi:10.1136/bmjopen-2020-040459 NELA Project Team. Fourth Patient Report of the National Emergency Laparotomy Audit (NELA). London: RCoA, 2018.	
British Heart	Comments form	Q1		**1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.**	Thank you for your comment. These recommendations support the prompt referral for assessment and treatment

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve Society				A key challenge for the management of HVD is the under-detection of significant HVD as highlighted by the OxValve study, delayed referral to for specialist assessment and delay in treatment. These areas need to be addressed by supporting networked based care, improving access to echocardiography in primary care, expanding specialist competency in HVD for doctors, nurses and clinical scientists, resourcing heart valve clinics. - There also needs to be clear stipulation of more rapid treatment pathways patients with severe symptomatic HVD. - A stipulated 2-week urgent review for symptomatic severe HVD would pose a challenge as it would need increased valve clinic resources to accommodate this. - In terms of 'challenging to implement', it will be very challenging to implement a policy in which surgical AVR is favoured over TAVI, especially if TAVI must be denied to certain patients that would clearly have been more suited for this. Elderly patients often have complex physical and also social needs and there can be non-medical reasons why a TAVI may be more appropriate for a patient (e.g. elderly person that is the main carer for their partner and wishes to return home and regain strength as rapidly as possible). It would be extremely challenging for clinicians across the country to deny TAVI to such patients if the current draft guidance is finalised.	by identifying the signs, symptoms and indications for referral and intervention. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Your comments will be considered by NICE where relevant support activity is being planned.
British Heart Valve Society	Comments form	Q2		**2. Would implementation of any of the draft recommendations have significant cost implications?** - Improved access to echocardiography - Increased number of physiologists / clinical scientists	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				- Increased number of healthcare professionals with competency in heart valve diseases - Resources for heart valve clinics and MDT meetings – which will need to be longer for discussion of a greater number of patients	
British Heart Valve Society	Comments form	Q3		**3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)** - Adopt recommendations made by GIRFT and the BHVS with regards to network-based care for heart valve disease, heart valve clinics and heart valve centres. - Flexible organisation of heart valve clinics with novel ways of working including virtual clinics for moderate HVD as most heart valve clinics will face the challenge of increasing patient numbers.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned.
British Heart Valve Society	Comments form	Q4		4. **The recommendations in this guideline were largely developed before the coronavirus pandemic. Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.** - The recommendation would be of particular harm to patients receiving treatment for severe AS in the context of COVID-19 - TAVI has substantial advantages over SAVR in the COVID-19 and post-COVID era, since there is no requirement for ICU, and hospital stay is far shorter. - This is reflected in the much greater fall in the numbers of SAVR cases done in 2020 than the fall seen for TAVI.	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				- This fall also means that the backlog of patients requiring treatment for severe AS is substantial. In 2020 there were 5600 fewer interventions for severe AS than expected. If the proposed guidelines were to be implemented, the proposed reduction in TAVI numbers and required increase in SAVR numbers would be a challenge to deliver. Even if it were theoretically possible to do this, the increase in ICU usage would have hugely negative implications in hospitals where ICU capacity is under enormous pressure. In contrast, TAVI allows patients to be treated quickly, with short hospital stays, and no use of ICU. If recommendations are implemented this would pose a real risk to patients waiting excessively for SAVR. Studies have shown up to 10% on excess waiting lists for AV intervention. It is inevitable that patients would die waiting for surgical aortic valve replacement if access to TAVI is restricted further than it already is – if anything, access to TAVI needs to be broadened at present to bring down waiting times for patients with symptomatic severe aortic stenosis.	should take the current context into account. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
British Heart Valve Society	Economic report TAVI	General	General	<u>BHVS Response to Economic Analyses Regarding Cost Effectiveness of TAVI</u> The BHVS has serious concerns about the methodology used to determine cost-effectiveness of TAVI – specifically, with regard to the *age* of the studies used. TAVI is a rapidly evolving field. The world's first TAVI procedure (2002) was not even performed 20 years ago. Over the past decade alone, TAVI has	Thank you for your comment. The model is now using data from the UK TAVI trial suggesting 0 days of ICU for TAVI patients at low surgical risk in the UK. ICU and hospital LOS in higher risks were calculated using the estimates of hospital resource predictors by Reinhoul

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				moved on leaps and bounds and the state of TAVI services across the UK today is unrecognisable from just a decade ago. As an example, in 2010 all TAVI procedures were performed with a general anaesthetic (requiring an anaesthetist present throughout the procedure), with transoesophageal echocardiography (requiring an imaging cardiologist throughout the procedure), many procedures were performed via the transapical [rather than transfemoral] route and a full cardiac theatre team including perfusionists and surgeons were on stand-by even for transfemoral cases. All patients went to intensive care after the procedure and length of stay in hospital was frequently more than one week. Patients had arterial lines, central venous lines and urinary catheters as a routine part of the procedure. This is vastly different from today, where the majority (>90%) of TAVI procedures are performed under conscious sedation via the transfemoral route, there is usually no need for an intensive care bed and, in many hospitals, patients walk out of hospital within 24-48 hours of the procedure. As a result, patients undergoing TAVI today very rarely require additional invasive lines such as an arterial line, a central venous line or a urinary catheter. Accordingly, associated patient discomfort and nosocomial infection (as well as cost) have been reduced by the substantial fall in use of these adjuncts. All complications from TAVI are significantly less frequent than they were a decade ago – including death, stroke, major vascular complication, heart attack, need for permanent pacemaker and significant paravalvular leak. This has largely been achieved by advances in technology. Specifically, the	(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/) The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. Results from recent trials - Leon 2021 and Popma 2019 - were added to the meta-analysis informing the treatment effects used in the model. In addition, in the base case we are using only treatment effects data coming from studies conducted on 2nd and 3rd generation to account for recent technological improvement. Baseline risks were revised to use contemporary UK data coming from the most recent (2019-2020) NICOR

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				size of the delivery sheath and adjustments/improvements to the TAVI valve design have contributed to reduced vascular access site-related complications and reduced paravalvular leak, respectively, and thus improved outcomes. The economic analyses have used trials that are, by modern standards, outdated. Furthermore, these trials used older TAVI valves that are no longer in use and thus complication rates based on these older valves are, by definition, irrelevant to modern practice. The quoted complication rates used (e.g. stroke rate of nearly 5%, paravalvular leak rate of nearly 5%) are much higher than those observed today. This is also true for the figures NICE have used for rate of pacemaker implantation, major bleeding and also valve re-intervention. The assumptions made regarding mean length of stay (LoS) both in hospital and in intensive care are, similarly, inconsistent with current practice. The NICE calculations use a presumed LoS of 6-8 days in hospital and 2-3 days in intensive care, both of which reflect past standards of care, not present. The overwhelming majority of TAVI procedures in the UK are performed via the transfemoral route under sedation and, unless there is an unexpected complication, these patients do not go to the intensive care unit at all. Thus, the use of an ICU stay of 2-3 days in cost-effectiveness modelling is inaccurate and would incorrectly increase costs associated with TAVI. The BHVS would suggest that NICE uses contemporary data – for example from the NICOR registry of all valves implanted in the UK – to determine the appropriate complication rates, lengths of stay and use of intensive	TAVI audit. Likewise, PVL rates were taken from studies of third generation valves (Sapien 3) and are in line with the rates reported in the TAVI registry. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				care beds. The NICOR registry captures all valves implanted across the UK and, we believe, provides a far more appropriate data to use for economic modelling and cost effectiveness analyses. For example, NICE could use data for all valves implanted between 2019-2020 inclusive. Finally, given that the cost-effectiveness of TAVI is directly related to the price of TAVI valves, we would strongly suggest that NICE puts forward a threshold cost price at which TAVI would become a cost-effective model. This may incentivise Industry to re-evaluate their cost price in the UK.	
British Heart Valve Society	Guideline	004	004	Many patients do not have a murmur and valve disease is also detected by offering echocardiography to patients with atrial fibrillation or a potentially cardiac symptom (Ref 1,2). We suggest that 'breathlessness' should specifically also include patients with COPD and disproportionate breathlessness and a raised BNP level. First degree relatives of people with a bicuspid aortic valve also have an approximately 10% chance of having a bicuspid valve and should be offered echocardiography. There needs to be greater access to echocardiography as recommended by the NHS long term plan (section 3.70) and this can be done by open access services, community echocardiography or, ideally, by a murmur clinic (ref 3). 1. d'Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J 2016; 37:3515-22	Thank you for your comment. Recommendation 1.1.1 now refers to atrial fibrillation. As there are numerous examples of how a person may present with breathless the committee did not want to add specific examples to the recommendation. BNP is referred to in section 1.3 on indications for interventions. First degree relatives of people with bicuspid aortic valve are also now referred to in the committee's discussion of the evidence in evidence review A. Service delivery including murmur clinics were not included in the scope of this guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. Chambers JB, Kabir S, Cajeat E. The detection of heart disease by open access echocardiography: a retrospective analysis. Brit J Gen Pract 2014;64:86-7. Draper J, Subbiah S, Bailey R, et al. The murmur clinic. Validation of a new method. Heart 2019;105:56-9.	
British Heart Valve Society	Guideline	004	010	Peripheral oedema is listed as a sign of significant valve disease, but this is a common and non-specific finding usually caused by incompetent veins or being overweight. It only occurs in end-stage left-sided valve disease or in the presence of severe tricuspid regurgitation when systolic waves in the neck or a pulsatile liver will be far more specific signs	Thank you for your comment. Although the guideline committee agrees that peripheral oedema is not specific for heart valve disease, echocardiography would avoid missing individuals with heart valve disease
British Heart Valve Society	Guideline	004	012	It may be difficult to assess the significance of a murmur (Ref 1) and most GPs do not feel adequately qualified and experienced to do this. The suggested advice about the second heart sound is beyond the competencies of most GPs and general physicians. However, there is good evidence that soft murmurs in the absence of symptoms are almost always normal. Echocardiography is the key investigation and should be requested if there is a *definite* murmur, especially if there are exertional symptoms or abnormal ECG. 1. Das P et al. The patient with a systolic murmur: severe aortic stenosis may be missed during cardiovascular examination. *Quart J Med* 2000; 93:685-8	Thank you for your comment. The first bullet point of 1.1.2 cover people with a murmur and abnormal ECG. Recommendation 1.1.3 cover people with a murmur and exertional syncope.
British Heart	Guideline	005	004	We are concerned about the length of the proposed timeframe (4 weeks) for patients with suspected syncope due to (critical) aortic stenosis to	Thank you for your comment. Recommendation 1.1.3 has been

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve Society				undergo echocardiography. The risk of dying is very high, within weeks (Ref 1,2). It would therefore be safer to offer echocardiography within 2 weeks at an absolute maximum and with adequate processes in place as contained in the British Heart Valve Society (BHVS) service delivery recommendations (Ref 3) it is expected that clinical assessment with one-stop echocardiography should be feasible within a week. 1. Malaisrie et al. Ann Thorac Surg 2014;98:1564-71 2. Pellikka P et al. JACC 1990;15:1012-17 3. https://www.bhvs.org.uk/bhvs-blueprint/	changed and now refers to within two weeks
British Heart Valve Society	Guideline	005	007	What is meant by 'consider urgent assessment for patients with a murmur and breathlessness or angina on minimal exertion or at rest'? Does this mean a referral to A and E? Chest pain at rest suggests an acute coronary syndrome rather than valve disease and should certainly receive immediate emergency attention.	Thank you for your comment. We now define urgent as two weeks but in accordance with current practice a person with very severe symptoms would be referred to accident and emergency
British Heart Valve Society	Guideline	005	017	1.1.6 Adults with mild valve disease do not require regular follow-up on an annual basis, but we are concerned that relying on a patient to develop symptoms could lead to certain patients being missed and presenting years later with advanced severe valve disease. It is well known that a percentage of patients with aortic sclerosis will progress to severe stenosis over a timeframe of 8-10 years. Patients with mild stenosis will also often progress to severe stenosis. A small proportion of patients with aortic sclerosis will progress to severe stenosis (1,2). Aortic sclerosis is common in older people (3) and these	Thank you for your comment. The committee have made a new recommendation to monitor people with mild to moderate valve disease every 3-5 yrs (1.4.2).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patients do not need follow-up. However, the presence of sclerosis in younger people (aged < 65) suggests that there are predisposing factors for calcific degeneration and these people also have a life-expectancy allowing more time for aortic stenosis to develop. These patients should have a repeat echo in 3-5 years. References 1 Cosmi JE et al. The risk of the development of aortic stenosis in patients with "benign" aortic valve thickening. Arch Int Med 2002; 162:2345-7. 2. Rosenhek R et al. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. Eur Heart J 2004; 25:199-205. 3) d'Arcy OxVALVE Study. Eur Heart J 2016; 37:3515-22.	
British Heart Valve Society	Guideline	006	003	Whilst we agree that patients with mitral prolapse and cardiac arrhythmias should be offered a specialist review, the current guidance is not specific whether this refers to arrhythmias that present by way of symptoms or should all patients with mitral prolapse (approximately 2-4% of the population) have ambulatory ECG monitoring? It would be helpful to clarify this point.	Thank you for your comment. Ambulatory ECG monitoring was not included in the scope of this guideline.
British Heart Valve Society	Guideline	006	007	We suggest that such guidance is not only useful to cardiologists, but also to obstetricians with a specialist interest in maternal heart health (or involved in the care of a pregnant woman with heart valve disease) and others involved in their care.	Thank you for your comment. We have deleted the line
British Heart Valve Society	Guideline	006	008	A discussion about contraception and family planning is important at the outset as soon as significant valve disease is diagnosed. We suggest this is emphasised in section 1.1.8	Thank you for your comment. We have made a new recommendation 1.1.9 to emphasise the importance of contraception and family planning

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Indeed, the NHS website itself states: (https://www.nhs.uk/pregnancy/related-conditions/existing-health-conditions/congenital-heart-disease/) "If you were born with a heart problem and you're planning to have a baby, talk to your cardiologist before you get pregnant." Thus, we feel that involving an appropriately trained cardiologist in the care of all such women is essential.	
British Heart Valve Society	Guideline	006 and general	010 and general	*There needs to be specialist advice for all patients with heart valve disease. This is part of the NHS long term plan (section 4.38). This needs to be in a dedicated heart valve clinic or with a cardiologist or other physician with competencies in valve disease allowing access to multidisciplinary team discussions (NHS plan section 3.70). Heart valve clinics are accepted as best practice models for delivering care and much work has been done in the UK to champion this.* *For women with child-bearing potential and heart valve disease, such advice should be essential and not merely 'considered'.* Mitral regurgitation caused by prolapse should be operated on by surgeons with specialist competencies in valve repair (as per GIRFT recommendations)	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'. Recommendation 1.9.4 recommends information and advice including on pregnancy. No evidence was identified on the level of expertise required to carry out intervention and due to variation in current clinical practice a consensus recommendation could not be made.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Heart Valve Society	Guideline	007	003	The BHVS believes that, if NICE wishes to address the role of pharmacological agents in heart valve disease, it would be prudent to break this down into the four main left-sided diseases seen in the UK. For example: <u>*Aortic Stenosis*</u> - The BHVS recommends that NICE should state explicitly that no trials have shown that statins alter the disease trajectory in aortic stenosis (and are not recommended as a 'treatment' of AS) - It is vital to control blood pressure in patients with aortic stenosis – ACE inhibitors can be used for hypertension in these patients. - Calcium channel blocking agents may increase mortality risk and should be avoided <u>*Aortic Regurgitation*</u> - Mixed results have been obtained in randomized trials that studied the effects of vasodilators such as calcium channel antagonists versus placebo – as such, calcium channel blockers are not recommended in normotensive patients on the grounds of 'treatment' of aortic regurgitation. <u>*Mitral Stenosis*</u> - Rate control with beta-blockers may help relieve symptoms. - Diuretics may help relieve symptoms and may well be required for patients not suitable for intervention. - Anticoagulation should be considered in patients with severe mitral stenosis, even if in sinus rhythm.	Thank you for your comment. The area prioritised for review in the guideline was the relative efficacy and safety of different pharmacological agents compared with each other or no treatment. Unfortunately, insufficient RCT evidence was found to support recommendations in this area except for beta blockers for adults with moderate to severe mitral stenosis and heart failure. No evidence was identified according to valve type and due to variation in clinical practice the committee were unable to make a consensus recommendation. As current clinical practice is variable the committee agreed to make research recommendations to promote further research in this area.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Mitral Regurgitation - Primary MR - We propose that NICE should discourage routine use of ACE inhibitors in normotensive patients purely on grounds of treatment of mitral regurgitation. - Secondary MR - We propose that NICE should emphasise here the importance of heart failure medications in patients with secondary mitral regurgitation	
British Heart Valve Society	Guideline	007	006	The section on heart failure with valve disease is surprisingly brief. Currently there is only a comment on patients with mitral stenosis – the least commonly encountered valve condition in the UK. There is no discussion on the use of other drugs for patients that develop left ventricular dysfunction and, in particular, on management of patients with severe valve disease that are not for intervention and will inevitably develop heart failure. It would seem appropriate here to suggest reference to the NICE guidelines on heart failure.	Thank you for your comment. The area prioritised for review in the guideline was the relative efficacy and safety of different pharmacological agents compared with each other or no treatment. Unfortunately, insufficient RCT evidence was found to support recommendations in this area except for beta blockers for adults with moderate to severe mitral stenosis and heart failure. As current clinical practice is variable the committee agreed to make research recommendations to promote further research in this area. A reference to the NICE guideline on chronic heart failure has been added (1.2.2).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Heart Valve Society	Guideline	008	008 - 013	An LV EF of 60% as a cut-off value has been chosen without justification but this must be based on retrospective observational research. There are no RCT proving that this cut-off is preferable to the current value of 50% recommended by all current international guidelines. We suggest that the conventional cut-off is retained pending further research. BNP is a non-specific marker of cardiac dysfunction and can be elevated in the elderly and in patients with other conditions such as atrial fibrillation. The experiences of our heart failure colleagues that run BNP clinics has shown that many elderly patients with an elevated BNP do not have significant cardiac problems. The BHVS has concerns about a BNP threshold which is only twice the upper limit of normal. There is a danger this will potentially commit many patients unnecessarily to further investigations and possibly unnecessary or premature valve treatment. The effective orifice area (EOA) measured by echocardiography is highly dependent on an accurate measurement of the left ventricular outflow tract diameter. This measurement is notoriously prone to error and many patients with moderate aortic stenosis may have a small EOA due to measurement error. We agree that *some* patients with EOA < 0.6cm^2 will indeed have very severe aortic stenosis, but many won't and this may, again, unnecessarily accelerate treatment. We would suggest that if this cut-off is to be used, a caveat is added (e.g. with an asterisk and explanatory footnote) that this measurement should be double-checked by an expert in echocardiography to ensure the reading is not artificially low due to technical error.	Thank you for your comment. The committee were made aware of limitations of the data from the HAVEC database for example incomplete data and therefore now place more emphasis on the Bohbot study. The cut-off in the recommendation has therefore been changed to 55%. The committee made the recommendation based on evidence specific to adults with known asymptomatic severe heart valve disease and the analysis was adjusted for age. Therefore, this recommendation is not intended to stratify patients presenting with symptoms but to triage patients with severe valve disease but no symptoms. For this specific population the GC believe the recommendation to be appropriate. However, we have added a note in the discussion that high BNP values are common with advanced age and this should be

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Unmasking of symptoms on exercise testing confirms the presence of symptomatic severe aortic stenosis and thus such patients should be referred on for intervention, not merely 'considered' for intervention. We suggest this point is removed from the list of other factors and a specific point that patients that claim to be asymptomatic should undergo exercise testing should be added (this would be consistent with international guidelines as well as current practice).	taken into consideration when decisions are made. An aortic valve area less than 0.6 cm^2 was also associated with increased all-cause mortality, both before and after valve intervention in adults with asymptomatic severe aortic stenosis. We added the point about double-checking the measurement to the committee's discussion of the evidence in evidence review D. There was limited evidence from only three studies of low and very low quality on stress testing in aortic stenosis and the committee discussed that the symptoms may or may not be due to the aortic valve. A recommendation therefore to consider referral was made, rather than a stronger offer recommendation. However, the strong offer recommendation 1.3.1, which was supported by a separate evidence review, includes people with severe aortic stenosis and symptoms

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unmasked by exercise that are believed to be caused by the aortic valve disease.
British Heart Valve Society	Guideline	008	014	There is no comment about how to manage patients with low-flow low-gradient aortic stenosis with a normal ejection fraction, so called "paradoxical low-flow low-gradient AS". This is an increasingly encountered cohort of patients, mostly elderly, and there needs to be a recommendation from NICE on treatment of this group as well as the conventional low-flow low-gradient (with depressed EF) cohort.	Thank you for your comment. No robust evidence was found to underpin a specific recommendation, however, the recommendation on use of CT calcium score when echo is not conclusive on the severity of the aortic stenosis is valid for these patients too. In the absence of a recommendation it is expected that current practice should continue.
British Heart Valve Society	Guideline	009	004 - 007	There is no published evidence for mid-wall fibrosis on MRI as an indication for intervention in aortic stenosis in the absence of symptoms or a reduced LV EF. The committee discussion is balanced and reflects our cumulative experience, but the recommendations go beyond this evidence. Randomised controlled trials such as Evolved are currently exploring whether MRI-guided care is superior to conventional care, but at present these trials are still recruiting and have not reported results, so we believe the current draft wording suggesting mid-wall fibrosis be used in decision-making is premature.	Thank you for your comment. We have made a recommendation for enhanced follow up for mid-wall fibrosis on MRI rather than as an indication for intervention.
British Heart Valve Society	Guideline	009	001	1.3.5 – we are unclear as to the rationale behind the comment regarding calcium in the valve if TAVI is being considered. Is this to ensure there is sufficient calcification for TAVI to proceed, or is to rule out extension of calcium into the left ventricular outflow tract that may increase risk of	Thank you for your comment. Although high calcium burden indicates severe aortic stenosis, extremely high calcium burden asymmetric distribution and calcium

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				annular rupture during valve deployment or influence the type of TAVI valve chosen (self-expandable rather than balloon expandable)?	burden in the left ventricular outflow tract increase the risk of the procedure and the likelihood of unwanted consequences like paravalvular leak. The committee agree with BCS that, indeed, high calcium burden and distribution in the entire aorta (eg porcelain aorta) should be part of the decision making. The committee did not suggest what decision the team should make in these cases, just highlighted the importance to take this into account. The committee anticipate that decisions are made based on multiple parameters to be considered for the individual patient.
British Heart Valve Society	Guideline	010	All	There is no discussion about tricuspid regurgitation (TR). Patients undergoing aortic or mitral valve intervention not infrequently require concomitant tricuspid valve repair and, sometimes, patients require isolated tricuspid valve surgery. It is not clear why this group of patients are not catered for in the current draft guideline. BHVS would suggest that NICE makes formal recommendations on this important subset of patients with heart valve disease.	Thank you for your comment. Unfortunately, no evidence was found on indications for interventions for tricuspid regurgitation. The committee has now made consensus recommendations on interventions for tricuspid regurgitation (1.5.14 and 1.5.15).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Heart Valve Society	Guideline	010	005	There is no RCT evidence for surgery in severe MR based on an LVSDi > 2.2cm/m^2. This threshold is suggested by retrospective analyses which are insufficient to change clinical management. The BHVs suggests to use a conventional cut off of 40mm for end-systolic diameter.	Thank you for your comment. LVSDI recommendation was based on two studies, one showing increased onset of symptoms/LV dysfunction and the other showing increased congestive heart failure, LV dysfunction or death. See the committee's discussion of the evidence in evidence review D. The recommendation is to consider referring and therefore not all referred patients would be offered surgery. The recommendation suggests PA pressure at rest >50 should be taken into account when deciding if there is an indication for surgery but the evidence was not strong enough to include as stand alone indicator
British Heart Valve Society	Guideline	010	006 - 011	The advice about the estimated PA pressure at rest is not clear. Does this say that a PA pressure > 50 mmHg at rest is an indication for surgery? Is this guideline saying that asymptomatic patients with non-repairable mitral valves should have surgery? The large difference in risk between repair and replacement has not been taken adequate account of. Repairability needs to be the first step in the assessment at this stage.	Thank you for your comment. We have edited recommendation 1.3.8 to refer to 'intervention' as we recommend both surgery and TAVI (1.5.8-1.5.10).
British Heart	Guideline	010	014	It is not safe to leave most patients with severe valve disease for a whole year between appointments. We know that they usually report symptoms	Thank you for your comment. Recommending more frequent follow-up will have a high impact on resource

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve Society				only when asked and do not seek earlier appointments should these develop. The committee should explain how patient discussion and echo findings would determine frequency of follow-up for patients with asymptomatic severe heart valve disease since this suggestion is not clear.	use, with little evidence to support its recommendation. If more frequent follow-up is required based on the individual's needs then this can still be arranged. Whilst the committee acknowledged that some patients only offer symptoms when in a cardiology appointment, this is not the case for all patients, many of whom present to the GP or cardiologist if they developed symptoms in between clinic appointments. Whatever frequency of follow-up is planned there is no way of predicting when patients will become symptomatic. The committee therefore agreed that flexibility is required, including to take into account the patient's likely ability to contact healthcare professionals if their symptoms change.
British Heart Valve Society	Guideline	011	007 - 012	This list of 5 bullet points does not include any reference to transcatheter aortic valve intervention (TAVI). There is quite widespread awareness of TAVI amongst patients as an option – often they or their relatives have performed online searches and will ask the question directly. Sometimes, a patient will bring a newspaper cutting to clinic to ask if this is appropriate for them. The fear of a sternotomy in an octogenarian is real.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				BHVS feels strongly that this should be acknowledged – we suggest adding to this list a sixth bullet point such as "the pros and cons of a transcatheter approach. Furthermore, the "risks associated with the procedure" should be changed to the "risks associated with the procedures" as more than one procedure is being discussed (surgical AVR via median sternotomy versus surgical AVR via minimal access route versus transcatheter valve intervention).	effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). Transcatheter has therefore been added to the bullet point on type of access in recommendation 1.5.1 as it is an option for people at high surgical risk. We now refer to procedure(s).
British Heart Valve Society	Guideline	011	005	Discussions about potential surgery need to start long before referral for intervention. Patient education leading to properly informed consent is one of the key roles of the specialist valve clinic. The patient and cardiologist need to discuss indications for surgery, symptoms to look out for and types of intervention possible. This then allows the patient to think, look up information, discuss with their GP or friends, and plan their life. It means that informed consent occurs potentially over many years and not just at the point when surgery is needed. Therefore, we suggest that the wording here is amended to reflect that this conversation should not be initiated for the first time once only intervention is indicated.	Thank you for your comment. Recommendation 1.9.4 recommends that people are offered information and advice on the any need for intervention and this could occur at any stage in the patient pathway including long before a referral for intervention is made.
British Heart Valve Society	Guideline	011	008	'Valve durability' must mean durability of the replacement valve. This should be clarified. Of note, most of the studies reporting on valve durability used an invalid definition (Ref 1) which conflated patient prosthesis mismatch and structural valve degeneration (SVD) thereby favouring TAVI over surgical valves. This definition has now been superseded by VARC-3 (Ref 2) which	Thank you for your comment. We have clarified that we mean prosthetic valve durability (recommendation 1.5.1).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				defines SVD by a combination of a change in cusp morphology, a rise in gradient and a fall in effective orifice area. 1. Capodanno D et al. Eur Heart J 2017;38:3382-90. 2. Genereux P et al. Eur Heart J 2021 in press There is little mid-term data on TAVI durability and no long-term data. It therefore remains uncertain whether TAVI will equal the durability of established surgical replacement valves. This is very important for the potential roll-out of TAVI to lower risk and younger patients.	
British Heart Valve Society	Guideline	012	003 - 007	The BHVS has significant concerns that the current draft guidance recommends one treatment over another (surgical over transcatheter valve replacement) and thus, as such, has removed the element of patient preference and patient choice from the management pathway. Shared decision-making is currently championed across the NHS on grounds of best practice and patient empowerment. The BHVS concurs that patients suitable for surgery should undergo surgery *if* this has been decided after a full discussion with the patient about all the treatment options available and their relative pros and cons in that particular individual's case. However, the current NICE draft guidance does not allow for this by discouraging the use of one treatment over another and is certainly counter to current practice and would, without question, represent a regressive step for our patients if this was the final opinion of NICE. In many centres across the UK, it has become commonplace for patients aged over 80 – for example – to be considered for transcatheter intervention (in preference to surgery) on grounds of reduced stay in hospital, avoidance of the need for sternotomy (and thus less pain), faster	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The committee agreed that patient choice and shared decision making should be an important part of this

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recovery and resumption of normal activities and a lower chance of needing admission to intensive care. However, the current guidance does not take into account the degree of risk from surgery ('suitable' vs 'unsuitable' does not clarify this) and is not consistent with the principles of shared decision-making, as there is no room for patient preference in the current draft document. It may be helpful to clarify exactly what is meant by 'unsuitable' and – specifically – whether this includes '*less* suitable'? For example, a cardiac surgeon may not feel that a patient is 'inoperable' but may feel that they are at relatively high risk for surgery and thus may be better suited to TAVI – this is already what happens in many instances and we believe it is crucial for patients that this practice can continue. Very few patients are truly 'inoperable' but – in many cases = patients may feel TAVI is a better option and to deny patients this would be damaging and, in our combined opinion, a very bad outcome for patient empowerment. The BHVS would recommend that point 1.5.3 is amended to state: "Offer aortic valve intervention for adults with symptomatic severe aortic stenosis, aortic regurgitation or mixed aortic valve disease. The choice of intervention (surgery or transcatheter treatment) should be discussed at a multi-disciplinary heart valve team meeting and patient characteristics as well as the patient's preferences should be accounted for in this process." Finally on the issue of surgery – it is not clear to the BHVS why minimally invasive AVR features so prominently? NICE's own evaluation (detailed in	guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). A cross reference to the NICE guideline on shared decision making has been added to 1.5.1. The definition of suitability for TAVI has been expanded on in the section 'terms used in this guideline'. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. Regarding the equal weighting given to minimally invasive and standard surgery, despite some clinically important harms of minimally invasive

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Evidence review H) is not favourable, either in terms of outcome or cost. No randomised trial has ever shown minimally invasive AVR to be superior to either surgical AVR or TAVI – yet mini surgical AVR is being treated as equivalent as conventional surgical AVR? The BHVS is not clear on the evidence NICE has used to promote minimally invasive AVR and would appreciate clarification of this issue. *Bicuspid versus non-bicuspid* It is not clear what NICE means when it states 'offer TAVI to patients with non-bicuspid aortic stenosis who are unsuitable for surgery' – what about patients with bicuspid valves that are unsuitable for surgery? It is highly likely that TAVI would offer them a superior outcome compared to medical therapy only. Although the data for TAVI in bicuspid valves are less robust than for patients with trileaflet valves, it is clear now from many registry studies that TAVI can be performed safely in many patients with bicuspid valves and this would be preferable to advocating a palliative approach, which is effectively what medical management of severe AS is. BHVS thus strongly recommends that NICE advocates that TAVI should be at least considered – if not offered – for patients with severe aortic stenosis of a bicuspid valve but are unsuitable for surgery.	surgery being identified across the included studies, and a health economic study that suggested minimally invasive surgery was not cost-effective compared with median sternotomy replacement, it was noted that all RCTs were small and for many outcomes only a small number of events were observed. The health economic study was also limited for the same reasons, as it was based on one of the RCTs included in the clinical evidence. It was also limited to a 12 month time-horizon, which may be too short to draw conclusions about cost effectiveness over a lifetime, though the committee agreed it is likely there would not be a large difference in outcomes after 12 months. In addition, the committee agreed that in their clinical experience there was no difference between minimally invasive and standard surgery replacement in terms of outcomes when performed by those with expertise in minimally invasive surgery, which could be supported by

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					a large amount of non-randomised evidence not included in this review of RCTs. It was agreed that the evidence included was insufficient to limit the use of minimally invasive surgery and a decision was made to offer either in those undergoing surgical replacement of the aortic valve, with the decision to be based on patient characteristics and preferences. Bicuspid aortic stenosis, was not included in the population in the study included in the evidence review. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated in this area.
British Heart Valve Society	Guideline	012	014	Whilst BHVS agrees that balloon mitral valvuloplasty is a suitable technique for treatment if rheumatic mitral stenosis, few such procedures are performed in the UK and thus individual operators may have very low procedural numbers (in many cases <5 per annum). In order to maintain expertise and thus minimise complications for patients, we would recommend that NICE comments here that such procedures should only be undertaken by experienced operators.	Thank you for your comment. It is not within the remit of NICE guidelines to specify the expertise of a person carrying out a procedure.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Heart Valve Society	Guideline	013	002	There is no comment in the mitral regurgitation section about discussion of such patients in an appropriate MDT. We would suggest NICE adds the phrase: "All patients being considered for mitral valve intervention should be discussed at a heart valve multidisciplinary team meeting"	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
British Heart Valve Society	Guideline	014	003	The current phrasing implies that patients with severe secondary mitral regurgitation should not be offered the possibility of edge-edge repair at all, which would be inappropriate if symptoms persist. The COAPT trial clearly demonstrated that the procedure can be of significant benefit in this patient cohort. Accordingly, the BHVS suggests that NICE modifies this sentence to state: "Transcatheter edge-edge repair should be considered in patients with severe secondary mitral regurgitation with heart failure who remain symptomatic despite optimal medical therapy"	Thank you for your comment. Transcatheter edge to edge repair may still be considered but after medical management has been tried first. We have added a recommendation to make this clearer (1.5.14).
British Heart Valve Society	Guideline	015	001	The section on anticoagulation and antithrombotic drugs (page 15 onwards) is surprisingly brief. There is no discussion about certain heart valves that can be used with a lower INR range (e.g. the On-X valve), no comments for general practitioners on how to manage patients with a mechanical valve that are found to have a low INR in the community (i.e. hospital admission for intravenous heparin versus increased dose of	Thank you for your comment. This topic was not prioritised for inclusion in the scope as there is very little variation in clinical practice in how people with mechanical valves are managed.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				warfarin with/without low molecular weight heparin cover) and, importantly, there is no statement that makes it explicitly clear that novel oral anticoagulant drugs (NOACs) should *not* be used in patients with mechanical valves. We strongly suggest that NICE add the sentence: "Do not use novel oral anticoagulant drugs in patients with mechanical heart valves"	
British Heart Valve Society	Guideline	015	002	The committee appears not to have considered the evidence of subclinical hypo-attenuated leaflet thickening (HALT) which occurs usually early after implantation in some 5% of biological replacement valves and nearer 15% of TAVI valves. This may lead to early obstruction and responds to anticoagulation using vitamin K antagonists or NOACs. One theory for the lower incidence of HALT in replacement valves is that these patients often receive warfarin for 3 months as recommended in international clinical guidelines. This is an area of great uncertainty but does at least need to be considered. Should all patients after TAVI have a CT scan looking for early leaflet thickening? Probably not but this is being discussed and it would be useful to have the opinion of NICE.	Thank you for your comment. No evidence was found on HALT and the committee were therefore unable to take this into consideration when making decisions on recommendations. The committee made a research recommendation.
British Heart Valve Society	Guideline	015	010 - 018	It is not clear how this list would be used to base decisions on follow-up frequency. Patients should have a point of contact with their specialist valve clinic (e.g. an e-mail address or telephone number). All patients with prosthetic heart valves / prior valve repair should have follow-up in a dedicated heart valve clinic rather than a general cardiology clinic and we believe this should be stated explicitly by NICE in this section on follow-up after intervention.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Prosthetic heart valve patients constitute a significant proportion of patients seen in heart valve clinics; there are many examples of this work being delegated to advanced nurse practitioners (ANPs), working under the supervision of a consultant cardiologist, and we believe this should be acknowledged by NICE and indeed would help with workforce planning for staffing of such clinics. Follow-up can be useful to reduce the risk of infective endocarditis by ensuring that dental surveillance is being undertaken and the need for antibiotic prophylaxis before invasive dental procedures is discussed as recommended by the Scottish Dental Clinical Effectiveness Programme advice (Ref 1) on implementing NICE guidance (Ref 2). There is no mention in the monitoring section on the NICE guidance around the use of antibiotic prophylaxis after heart valve surgery. The BHVS would recommend that NICE references its prior publication on this issue in this document, as it is pertinent. 1. https://www.sdcep.org.uk/published-guidance/antibiotic-prophylaxis/ 2. NICE clinical guidelines 64. Follow-up may also pick up a new arrhythmia (particularly atrial fibrillation) in a patient with a biological valve, which therefore leads to a significant change in management by initiating anticoagulation.	
British Heart	Guideline	016	021	This section states that patients should be given information about how to access palliative care services. A heart valve clinic should help the patient with this (Ref 1).	Thank you for your comment. Service delivery including heart valve clinics

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve Society				1. Lancellotti P, Rosenhek R, Pibarot P, et al. Heart valve clinics: organisation, structure and experiences. Eur Heart J 2013;34:1597-1606.	were not included in the scope of this guideline.
British Heart Valve Society	Guideline	General		Clinicians caring for patients with valve disease should have specialist competencies in valve disease. There is abundant evidence that results improve with expertise and volumes (Ref 1) and specialist competencies are integral to the GIRFT recommendations. Chambers JB. Valve clinic: why, who and how? Education in Heart. Heart 2019; 105:1913-20.	Thank you for your comment. No evidence was identified on the level of expertise required to carry out the intervention and due to variation in current clinical practice a consensus recommendation could not be made.
British Heart Valve Society	Guideline	General		Recognised best practice is for patients with valve disease to be cared for in specialist valve clinics where clinicians have appropriate competencies, there are organisational arrangements like one-stop echocardiography and clear referral patterns to interventional cardiologists and surgeons. There should also be links to related specialties within cardiology like electrophysiology and heart failure and outside cardiology like elderly care and chest medicine.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.
British Heart Valve Society	Guideline	General		Heart valve networks should be established between cardiothoracic units, their feeding district hospitals and the community.	Thank you for your comment. Service delivery including heart valve networks were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					assessment may be provided in the section 'terms used in this guideline'.
British Heart Valve Society	Guideline	General		An opinion from a cardiologist should be provided for all patients admitted with decompensated heart valve disease or infective endocarditis. A district general cardiologist should discuss transfer of these cases with the multidisciplinary team at the cardiothoracic centre.	Thank you for your comment. The scope of this guideline focused on monitoring where there is no indication for intervention and indications for interventions to ensure that people with heart valve disease are managed optimally. The committee made recommendations on those indications with evidence to support their use. Infective endocarditis was outside of the scope of the guideline. However, the recommendations do not preclude a cardiologist opinion being sought for people admitted with decompensated heart valve disease or infective endocarditis. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					'terms used in this guideline' and cite MDTs as an example of how this may be provided.
British Heart Valve Society	Guideline	General		Heart valve centres should have appropriate infrastructure and resources to implement best practice guidelines, specialist heart valve teams comprising multidisciplinary expertise delivering integrated care pathways, clear referral pathways into the centre and excellent communication with all clinicians involved with the patient's care, multidisciplinary perioperative management. They should ensure collection of detailed outcome data for internal and external audit. These standards are part of the GIRFT recommendations and are accepted by international guideline documents. 1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Europ Heart J 2017;38:2739-2786. 2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2020; Dec 17:[Epub ahead of print]. Chambers JB, Prendergast B, Iung B, Rosenhek R, Zamorano JL, Pierard LA, Modine T, Falk V, Kappetein AP, Pibarot P, Sundt T, Baumgartner H, Bax JJ, Lancellotti P. Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee support the collection of audit data and this is now mentioned in the committee's discussion of the evidence if evidence review H.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Cardiothoracic Surgery Viewpoint. *Europ Heart J 2017;*38:2177–83. https://doi.org/10.1093/eurheartj/ehx370 and Eur J Cardiothorac Surg 2017;52:418-24.	
British Pharmaceutical Society – BNF Publications	Guideline	015	001	BNF notes that no recommendations are made for anticoagulation and/or antiplatelet therapy if a mechanical heart valve is used for valve replacement surgery. Was this omission deliberate? The guidance could currently be interpreted to assume that no anticoagulation and/or antiplatelet therapy is required with a mechanical heart valve.	Thank you for your comment. This topic was not prioritised for inclusion in the scope as there is very little variation in clinical practice in how people with mechanical valves are managed.
British Society of Endocardiography	Guideline	004 and 005	003 onwards	Whilst we accept that NICE guidance is developed for clinical excellence and is not designed to address workforce issues, we believe that it is vitally important to ensure that patients with suspected or known valve disease are diagnosed / monitored most effectively. As such, we recommend that this guidance introduces the use of diagnostic echocardiography hubs and specialist echocardiography heart valve clinics. As a Society we feel that these patients should be diagnosed / monitored by experienced echocardiographers who have specific training in the assessment of these patients. We also recommend that these patients can be assessed in clinics which may be located in community settings closer to the patient's home – with the overarching clinical and diagnostic governance of an established heart valve clinical team.	Thank you for your comment. Service delivery including diagnostic hubs were not included in the scope of this guideline.
British Society of Endocar	Guideline	005	017	Whilst we acknowledge that mild valve disease would essentially never be responsible for important cardiac symptomology and the BSE agree that specialist assessment is not required for such individuals, we do have a concern regarding the lack of advice to pursue echocardiographic surveillance in such patients.	Thank you for your comment. The committee have made a new recommendation to monitor people

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
diography				This is particularly the case with mild AS, which will necessarily progress with time. In large registry data around 20% of individuals with mild AS at inclusion required surgical intervention within 5 years (Ref 1,2) Nor can we rely on patients developing 'symptoms' to ensure that they seek timely medical attention. As is highlighted elsewhere within this NICE proposal, there are multiple reasons to consider intervention in patients with genuinely asymptomatic severe AS (including reduced LVEF, or very high gradients). Such individuals, by definition, have no symptoms, therefore they would not 'self-present' and yet could very easily have evidence of adverse prognostic findings. We would fully agree that such patients do not need intensive review, but we would tentatively suggest that interval echo surveillance is advised: this would not be resource intensive and yet ensures that individual patients are not exposed to unnecessary risk. With regards aortic stenosis, international guidelines and the recently published BSE guidance for aortic valve disease advocates echo surveillance every 3-5 years for mild AS (Ref 3,4,5) and we would urge the NICE committee to adopt such a suggestion. 1. Otto CM, Burwash IG, Legget ME et al Prospective Study of Asymptomatic Valvular Aortic Stenosis. Circulation. 1997; 95:2262–2270. 2. Rosenhek R. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. Eur Heart J. 2004; 25:199–205. 3. Ring L, Shah B, Bhattacharyya S. Echocardiographic Assessment of Aortic Stenosis: a practical guideline from the BSE. ERP March 2021.	with mild to moderate valve disease every 3-5 yrs (1.4.2).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				4. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 5. Otto C, Nishimira R, Bonow R et al. 2020 ACC/AHA Guideline for theManagement of Patients WithValvular Heart Disease. J Am Coll Cardiol. 2020;:1–173.	
British Society of Endocardiography	Guideline	006	003	Given the risk of SCD in those with arrhythmic MVP, BSE recommend that referral for specialist assessment in those with bi-leaflet prolapse should include not only those with documented ventricular arrhythmia, but also those with either unexplained seated/supine or exertional syncope. 1. Miller MA, Dukkipatti SR, Turagam M, Liao SL, Adams DH, Reddy VY. Arrhythmic Mitral Valve Prolapse (2018). Journal of the American College of Cardiology; 72:2904-14	Thank you for your comment. Recommendation 1.1.3 covers exertional syncope which should be referred irrespective of the presence of mitral valve prolapse.
British Society of Endocardiography	Guideline	006	004	Although TTE is the first line in the assessment of MV disease, when echo windows are limited or further clarification in aetiology, mechanism and reparability of the valve lesion is needed, TOE should be recommended. 1. *Robinson S, Ring L, Augustine D, Rekhraj S, Oxborough D, Lancellotti P and Rana B. The Assessment of Mitral Valve Disease: A guideline from the British Society of Echocardiography (2021) - in print.*	Thank you for your comment. In the absence of evidence and variation in clinical practice the committee were unable to make a recommendation on TOE. However, the recommendation does not preclude TOE being used in the circumstances you describe.
British Society of Endocardiography	Guideline	006	004	The BSE recommend guidance for urgent surgery in those with acute severe mitral regurgitation 1. Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal 38 (36): 2739-2791.	Thank you for your comment. We did not find any evidence for acute mitral regurgitation and so no recommendations were made for this population. However, the guidelines do not advise against urgent surgery

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					in this group. Therefore, current practice can continue.
British Society of Echocardiography	Guideline	007	001	Systemic hypertension exacerbates left sided valve disease, especially AR, AS and MR, and is associated with worsening symptoms – our new guidelines (1) recommend BP control prior to assessment of valve disease. The guidelines could make recommendations for management of hypertension as this could alter the echocardiographic parameters that are assessed. 1. Ring L, Shah B, Bhattacharrya S, Harkness A, Belham M, Oxborough D, Pearce K, Rana BS, Augustine DX, Robinson S, Tribouilloy C. Echocardiographic assessment of aortic stenosis: a practical guideline from the British Society of Echocardiography. Echo Research and Practice. 2021; March 1.	Thank you for your comment. The management of hypertension was not prioritised as a topic for inclusion in the scope for this guideline.
British Society of Echocardiography	Guideline	008 and 029	010 and 011	The BSE commends the NICE committee with regards its review of the LVEF value that should prompt consideration of AVR in patients with aortic stenosis. The BSE has some concerns about the proposed threshold. Prominent amongst the data used to derive the proposed guidance is a study from the HAVEC database(1). The HAVEC database is the amalgamation of several European echo databases. Given the nature of data collection, we cannot be sure of a consistent clinical approach across all centres. A very large proportion of individuals (22%) had incomplete data regarding LVEF or even the severity of AS. Whilst these patients were not included in the final analysis, this very fact highlights a potential lack of robustness, which should be accounted for when interpreting the data. Whilst baseline echo is reported, follow-up data for both echocardiographic findings and clinical status is sorely lacking, importantly including whether	Thank you for your comment. We have changed recommendation 1.3.2 to 55%. The HAVEC data and Bohbot papers were included in the review. The remaining papers were not included because two were not specifically in asymptomatic severe AS (they do not provide adjusted results for LVEF), one paper does give results for asymptomatic severe patients but not using thresholds of LVEF and the remaining two references either cite the BSE

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the patients had developed symptoms. Minimal information is offered pertaining to decisions regarding the timing of intervention. Of patients with severe AS at study entry, just 45% underwent AVR surgery during follow-up, which seems a low proportion given that outcomes are reported up to 96 months after study entry. Compare this to the analysis by Bohbot et al(2) in which more than 75% of comparable individuals underwent intervention within the follow up period. Even more fundamental: patients who did undergo surgery did so at an average of 1 year after inclusion, but the echo data immediately prior to surgery is not reported. It is extremely likely that echocardiographic The BSE commends the NICE committee with regards its review of the LVEF value that should prompt consideration of AVR in patients with aortic stenosis. The BSE has some concerns about the proposed threshold. Prominent amongst the data used to derive the proposed guidance is a study from the HAVEC database(1). The HAVEC database is the amalgamation of several European echo databases. Given the nature of data collection, we cannot be sure of a consistent clinical approach across all centres. A very large proportion of individuals (22%) had incomplete data regarding LVEF or even the severity of AS. Whilst these patients were not included in the final analysis, this very fact highlights a potential lack of robustness, which should be accounted for when interpreting the data. Whilst baseline echo is reported, follow-up data for both echocardiographic findings and clinical status is sorely lacking, importantly including whether the patients had developed symptoms. Minimal information is offered pertaining to decisions regarding the timing of intervention. Of patients with severe AS at study entry, just 45% underwent AVR surgery during follow-up, which seems a low proportion given that outcomes are	guideline or are used to reference the percentage of deaths that occur in asymptomatic severe AS (they are not prognostic).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				reported up to 96 months after study entry. Compare this to the analysis by Bohbot et al(2) in which more than 75% of comparable individuals underwent intervention within the follow up period. Even more fundamental: patients who did undergo surgery did so at an average of 1 year after inclusion, but the echo data immediately prior to surgery is not reported. It is extremely likely that echocardiographic parameters would have changed in the time between study entry and surgery, and therefore it is problematic to associate an LVEF finding 1 year prior to surgery with long-term outcomes. On a very simple analysis, an LVEF<60% was associated with poorer outcomes for the entire cohort. However, this analysis includes the 55% of patients with severe AS who were not offered intervention. Out of a total of 123 deaths, more than half occurred in patients who were never offered AVR. To put this number into perspective: previous reports largely agree that the rate of cardiovascular death in genuinely asymptomatic severe AS is somewhere between 0.5-2% per annum(3). Within the HAVEC data, the rate of cardiovascular death within the apparently 'asymptomatic' patients was almost 14%. In our collective experience, it is extremely rare for patients with apparently asymptomatic aortic stenosis to die suddenly of heart failure as is reported within this study. A much more likely conclusion is that a large proportion of these deaths actually occurred in symptomatic individuals and this is a limitation that is acknowledged by the authors themselves within the study. We believe that caution needs to be exercised if conclusions from the HAVEC data are to be applied to genuinely asymptomatic individuals.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				A more pertinent analysis would be if we examine only those individuals with severe AS who ultimately underwent AVR. Interestingly, in this scenario, a pre-operative LVEF of<60% was not independently associated with poorer long-term survival. There are other studies examining the association of LVEF and survival in severe AS, which the committee may wish to consider. Dahl et al(4) report on more than 2000 individual patients identified with high gradient AS, all of whom underwent AVR. The long-term post operative survival was shown to be lower in patients when the pre-operative LVEF was 50-59% in comparison to patients in whom the pre-operative LVEF was ≥60%. This association was seen to be independent of all other clinical and echocardiographic criteria, including the presence of symptoms. Even when patients with no Class I or Class IIa indications for intervention were analysed separately (albeit this representing a much smaller sample of just 250 patients), the association between a preoperative LVEF 50-59% and reduced survival was maintained. A large Japanese database has also reported on the association between LVEF and long-term survival in patients with severe AS(5) Amongst a large cohort of patients, an LVEF 50-59% was associated with poorer 5-year survival and higher rates of heart failure than when LVEF was noted to be □60% at study entry. Unfortunately, it is difficult drawing substantial conclusions from this study on the basis that there was a very low rate of aortic valve intervention: of 1989 patients with severe AS and symptoms at study entry, only 60% were offered surgery, with the remaining 40% being offered medical therapy. Clearly, we cannot use this data in isolation to suggest a change in management to genuinely asymptomatic individuals with severe AS.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The above listed studies divide patients according to LVEF but with relatively large strata: patients with an LVEF of 50-59% were 'grouped together'. This approach runs the risk of mis-identifying the 'true' threshold of LVEF that is associated with adverse outcomes. More recent work by Bohbot et al(2) addressed the same question, and includes >1600 patients, all with severe AS who were either asymptomatic or minimally symptomatic at inclusion. Patients were then divided into three strata: an LVEF 50-55%; an LVEF 55-60%, or an LVEF>60%. Long-term survival was significantly worse in those patients with an LVEF 50-55%. There was no significant difference between the observed 5-year survival rates in those patients with an LVEF 55-60% compared to patients with an LVEF>60% (72□2% vs. 74□2%). If we examine only those patients who underwent surgery, the analysis is even more persuasive. All 'surgically' treated patients underwent intervention within 3 months of study entry and therefore the echocardiographic findings are unlikely to have significantly changed in the intervening time. Those patients with an LVEF<55% had poorer long-term survival, whereas those with an LVEF 55-59% had identical long-term survival to those with an LVEF>60%. In fact, there was no difference in long-term outcomes if patients with an LVEF 55-60% were compared to those with an LVEF >70%. This study would therefore seem to suggest that the LVEF threshold that identifies high-risk is 55% (and not 60%)(2). The conclusions drawn from this paper by Bohbot et al does not disagree with the earlier studies listed above, but rather refines the echocardiographic threshold criteria. It becomes clear that if we 'group together' patients with an LVEF 50% with individuals in whom an LVEF 59% is obtained, overall outcomes will be	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				worse, but appear to largely be driven by the patients within the 50-55% sub-group. The NICE committee also comment on changes in LVEF as an adverse predictor of outcome, and allude to the fact that once LVEF is seen to drop below 60%, it rapidly declines further (thereby supporting the perspective of intervention at an LVEF threshold of 60%). We would add caution to this statement. Some database analyses suggest that large and rapid reductions in LVEF (of >10% per annum) are occasionally seen in patients with severe AS and appear to be associated with poorer outcomes. However, such reductions in LVEF% were noted to occur equally frequently in patients with an initial LVEF>60% as with those patients in whom the LVEF was <60% on baseline assessment(6). In essence: the index LVEF value is not of itself a predictor of subsequent LVEF decline and therefore an isolated LVEF value cannot be used in and of itself to justify intervention. For these reasons, we would tentatively suggest an adjustment to the proposed NICE guidance. We believe that an LVEF<55% has clear evidence for adverse outcomes, whereas the data supporting a threshold of <60% is contradictory. We believe that the data seems to justify a more robust recommendation from NICE, whereby surgery is 'offered' to patients with asymptomatic severe AS and an LVEF<55%. The recently published guidance from the BSE identifies an LVEF<55% as a high-risk characteristic in asymptomatic severe AS(7). 1. Lancellotti P, Magne J, Dulgheru R et al. Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. JAMA Cardiology 2018:1–9.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. Bohbot Y, de Meester de Ravenstein C, Chadha G, et al. Relationship Between Left Ventricular Ejection Fraction and Mortality in Asymptomatic and Minimally Symptomatic Patients With Severe Aortic Stenosis. JACC Cardiovasc Imaging. 2019; 12:38–48. 3. Iung B. Management of asymptomatic aortic stenosis. Heart. 2010; 97:253–259. 4. Dahl JS, Eleid MF, Michelena HI, Scott CG, Suri RM, Schaff HV, Pellikka PA. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. Circulation: Cardiovascular Imaging. 2015; 8 5. Kimura T, Taniguchi T, Shiomi H, et al. Prognostic Impact of Left Ventricular Ejection Fraction in Patients With Severe Aortic Stenosis. JACC: Cardiovascular Interventions. 2018; 11:145–157. 6. Minamino-Muta E, Kato T, Morimoto T et al. Decline in Left Ventricular Ejection Fraction During Follow-Up in Patients With Severe Aortic Stenosis. JACC: Cardiovascular Interventions. 2019; 12:2499–2511. 7. Ring L, Shah B, Bhattacharrya S et al. Echocardiographic assessment of aortic stenosis: a practical guideline from the British Society of Echocardiography. Echo Research and Practice. 2021; March 1.	
British Society of Endocardiography	Guideline	008	014	We compliment the NICE committee for attempting to summarise a phenomenally complex area. However, the BSE has some concerns with these statements as they stand. In our opinion, they do not appear to be complete, and if they are as intended, there appear to be errors of fact. Recommendation 1.3.3 refers to the clinical scenario of low-flow low-gradient aortic stenosis. Although the statement does not define what is meant by this, within cardiological practice this scenario is usually characterized by an aortic valve area (AVA) of <1cm2, thereby implying	Thank you for your comment. Regarding the terminology, we have now labelled this group as symptomatic low-gradient aortic stenosis with LVEF less than 50%. In response to your specific comments:

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				severe AS, combined with a mean gradient of <40mmHg, suggesting non-severe AS. One important explanation for such an observed discrepancy is a reduction in cardiac output or flow, which may occur in patients with impaired LV systolic function. Furthermore, whilst historically this scenario has often been labeled as 'low flow', in actual fact, none of the original reports of this phenomenon actually required an assessment of 'flow' as inclusion criteria on the assumption was that flow was low (owing to the presence of reduced LVEF). For this reason, the BSE (and others) have chosen to simplify the terminology, and refer to this phenomenon as 'low-gradient AS with impaired LVEF'(1). The principle that patients with impaired LVEF may present with discrepant indices of AS severity is well described in historical cardiological practice(2-5) In essence, there are two potential explanations for the echocardiographic observations: • A patient with 'truly severe AS' who has reduced cardiac output or flow may display Doppler indices of AS severity (such as mean gradient) that are lower than expected for the degree of valvular obstruction and therefore the AS severity is underestimated. If we solely relied on mean gradient, this would result in some patients who may benefit from AVR being denied intervention. • Conversely, 'pseudo-severe AS' refers to a patient with non-severe AS. In the presence of reduced flow, a relatively compliant aortic valve will not fully open. In this situation the measured aortic valve area is low, but overestimates AS severity, potentially resulting in some patients being referred for intervention where it is not required (and thereby exposing them to unnecessary risk).	1. Thank you for raising the point. The GC believe that an LVEF threshold of <50% is appropriate for the recommendation as otherwise it is unclear what to do for people with LVEF 40-50%. The only minor disadvantage is the people with EF 40-50% may undergo DSE which they do not require. However the committee noted that the DSE would not alter the assessment of AS severity (and therefore result in them undergoing intervention unnecessarily) because the DSE would almost certainly provide the same result as the conventional echocardiogram (moderate rather than severe AS). 2. We agree with your point and have reworded the recommendation as follows: Consider referring adults with symptomatic low-gradient

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The management of the two clinical scenarios described above is fundamentally different and therefore a method is needed to help separate these two entities. The best described method is Dobutamine Stress Echocardiography (DSE). Specific comments: 1. Our first comment is regarding the threshold value of LVEF in which DSE could be considered: 1.3.3 Consider referring adults with symptomatic low-flow low-gradient aortic stenosis with LVEF less than 50% for intervention if they have all of the following: As we are sure the NICE committee are aware, in the published literature describing the use of DSE for the assessment of 'low-flow low-gradient AS', the vast majority of included patients had values of LVEF that were less than 40% (and usually less than 35%)(6-16). There are extremely rare reports of individuals with LVEF values between 40-50% undergoing DSE for this clinical scenario, totaling fewer than 10 patients(17,18), although some later database analyses may also include some examples of such patients. The reason for this is that very minor reductions in LVEF to 48-49% (for example) are unlikely to significantly reduce flow sufficiently to result in discrepant indices of AS severity, and advocating DSE in such patients is unlikely to provide value. Nevertheless, international guidelines have frequently taken the view that any patients with low-gradient AS and an LVEF<50% could be considered for DSE(19,20). Whilst we do not think this approach is necessarily unreasonable, it is important to appreciate the	aortic stenosis with LVEF less than 50% for intervention if during dobutamine stress echocardiography they have a mean gradient across the aortic valve which increases to >40mmHg combined with an aortic valve area that remains <1cm^2. 3. We agree with your point about the definition of 'true severe' and have reworded the recommendation as noted above. However, in the absence of evidence on projected EOA the committee agreed that this should not currently be included in the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				rationale and evidence, and within the recently published BSE guideline document, this challenging group is discussed and specific guidance is provided(1). 2. Our second comment regards the following bullet point: - a mean gradient across the aortic valve less than 40 mmHg on echocardiography 'Low-flow low-gradient aortic stenosis' by definition requires that the mean gradient is <40mmHg. If the mean gradient were >40mmHg, such a patient has unequivocal evidence of severe AS. In that context, the patient would already have an absolute mandate for aortic valve intervention in international guidelines (as the LVEF is <50%)(19,20), and indeed such a patient would already fulfill NICE guideline statement 1.3.1 (offer an intervention to adults with symptomatic severe heart valve disease) AND NICE guideline statement 1.3.2 (Consider referring adults with asymptomatic severe aortic stenosis for surgery, if suitable, if they have an LVEF<60%). Therefore, DSE would be both completely unnecessary and potentially harmful. As such this bullet point is superfluous and should be removed. 3. We also have comments regarding the statement around the use of DSE: 'a valve area less than 1.0 cm2, which does not increase on DSE'	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				DSE as a method to separate 'true-severe' from 'pseudo-severe' AS has been utilized for around 25 years. Although different methodologies have been described within the literature, in essence the principle is to use Dobutamine to improve cardiac output (and therefore flow), which results in indices of aortic stenosis severity that are easier to interpret, thereby facilitating clinical decision-making. The method was first described clinically by deFillipi et al(17), but has been replicated in many publications and is now widely used worldwide(6-8, 11, 12, 15, 16, 17) The BSE recognizes and accepts the limitations of the data pertaining to DSE in this scenario. Published studies usually involve small number of patients, there is no randomization, clinical decision making is not immediately transparent with the potential for bias and there are high rates of co-incidental co-morbidities including coronary artery disease which may influence the observed outcomes. Nevertheless, there is a consensus approach in all studies in that 'true-severe' AS is usually defined as both an AVA that remains <1cm2 combined with a mean aortic gradient that exceeds (or is very close to) 35-40mmHg after dobutamine stress. To the knowledge of the BSE there are no significant studies that define true-severe AS only according to the AVA after DSE and an interpretation of the mean gradient at peak stress is an absolutely essential component of the DSE study.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The methodology of using Dobutamine to augment cardiac output and re-evaluate aortic stenosis indices has also been replicated and described during cardiac catheterization, where again a combination of both the calculated AVA and the mean gradient were essential to the outcomes observed21. On the basis of this consistent clinical approach, international guidelines that describe the use of the DSE in the scenario of low-flow low-gradient AS similarly dictate that both AVA <1cm2 and a mean gradient >40mmHg are required for the diagnosis of true-severe AS(19, 20). The BSE have recently published guidance on the echocardiographic assessment of aortic stenosis in which the data and methodology is extensively discussed(1). The reason that both AVA and mean gradient are important in the interpretation of DSE is as follows: a significant minority of patients do not demonstrate an increase in cardiac output with dobutamine stress (referred to as a 'lack of flow reserve'), and therefore the obtained echocardiographic indices do not substantially change after DSE. Such patients are considered one of the most challenging subsets of this group when it comes to decision-making. As the NICE recommendations currently stand, the diagnosis of true-severe AS would therefore become over-diagnosed, potentially leading to some individuals being referred for unnecessary aortic intervention. We wonder whether the NICE statement was alluding to the concept of the projected effective orifice area (Proj-EOA), which can be derived using the projected flow rate methodology. This methodology was initially described	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				in 2006 as part of the TOPAS initiative, and has been subsequently replicated and validated, and now forms the basis of a large international registry(9, 10, 13-15, 22). Projected effective orifice area was developed to help with the challenges of interpreting DSE in patients with low-flow low-gradient AS and is particularly useful in patients who do not fulfill the conventional criteria for severe AS after DSE, or those patients with a lack of flow reserve. The Proj-EOA has been shown to outperform other resting and stress echocardiographic criteria for the identification of true-severe AS(9, 10, 22). Historically, patients that displayed a lack of flow reserve with DSE were observed to have extremely high rates of cardiovascular mortality during aortic valve surgery(8, 11, 23). In part this is because differentiating 'true-severe' from 'pseudo-severe' in patients without flow reserve is extremely challenging and therefore it is very likely some individuals without severe AS were exposed to cardiac surgery unnecessarily. In the current era where TAVI is increasingly used, Proj-EOA has been reported to not only identify individuals that benefit from intervention, but also demonstrates that patients perform similarly well irrespective of the presence or absence of flow reserve(13) (suggesting a consistent clinical benefit when identifying such patients using this methodology). Even in a subset of patients with very poor LVEF at inclusion (<30%), similar improvements in LVEF after TAVI intervention was seen irrespective of the presence of flow reserve when patients were selected for intervention according to the Proj-EOA(14).	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				A recent report highlighting the experience of DSE in patients with low-flow low-gradient AS compares the value of the more conventional DSE approach and the Proj-EOA method. Sato et al(15) report that patients with 'true-severe AS' (identified using conventional DSE criteria) did better with AVR than without, which is very much as we would expect. This benefit remained after correction for confounding factors. However, there was an apparent small but significant improvement in survival with AVR in patients with indeterminate AS and also 'pseudo-severe' AS when defined using conventional DSE criteria. When the included patients were re-defined according to the Proj-EOA method, aortic valve intervention was only seen to be beneficial in those considered to have 'true-severe' AS, suggesting that the Proj-EOA technique is an excellent discriminator of benefit within these challenging patient cohorts. To date, the Proj-EOA method has been reported in the literature in more than 500 patients from different cardiological centres with a broad range of co-morbidities and has consistently been shown to identify patients who benefit from aortic valve intervention(9, 10, 13-15, 22). The recently published BSE guidelines on the assessment of aortic stenosis also discuss the merits of the Projected effective orifice area methodology and have included this technique within our protocol(1). The BSE would therefore suggest an adjustment to the wording within recommendation 1.3.3. as follows: Consider intervention in patients with severe low-gradient AS with an LVEF <50% if one of the following are present:	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• During DSE, a gradient across the aortic valve which increases to >35-40mmHg, combined with an AVA that remains <1cm2 at any time or • A projected-EOA of <1cm2 Given the complexities of this clinical scenario, we would urge the NICE committee to reference and signpost the BSE guidance within the NICE recommendations, which include detailed description of the methodology and interpretation of both conventional DSE and Projected-EOA, a summary of the evidence in this scenario, and the optimal identification of pseudo-severe AS(1). 1. Ring L, Shah B, Bhattacharrya S et al. Echocardiographic assessment of aortic stenosis: a practical guideline from the British Society of Echocardiography. Echo Research and Practice. 2021; March 1. 2. Zoghbi WA, Farmer KL, Soto JG et al. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. Circulation. 1986; 73:452–459. 3. Oh JK, Taliercio CP, Holmes DR et al. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: Prospective Doppler-catheterization correlation in 100 patients. J Am Coll Cardiol. 1988; 11:1227–1234.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				4. Burwash IG, Thomas DD, Sadahiro M et al. Dependence of Gorlin formula and continuity equation valve areas on transvalvular volume flow rate in valvular aortic stenosis. Circulation. 1994; 89:827–835. 5. Voelker W, Reul H, Nienhaus G et al. Comparison of valvular resistance, stroke work loss, and Gorlin valve area for quantification of aortic stenosis. An in vitro study in a pulsatile aortic flow model. Circulation. 1995; 91:1196–1204. 6. Schwammenthal E, Vered Z, Moshkowitz Y et al. Dobutamine echocardiography in patients with aortic stenosis and left ventricular dysfunction: predicting outcome as a function of management strategy. Chest. 2001; 119:1766–1777. 7. Monin J-L, Monchi M, Gest V et al. Aortic Stenosis With SevereLeft Ventricular Dysfunction andLow Transvalvular Pressure Gradients. J Am Coll Cardiol. 2001; 37:2101–2107. 8. Monin J-L, Quéré J-P, Monchi M et al. Low-Gradient Aortic Stenosis. Circulation. 2003; 108:319–324. 9. Blais C, Burwash IG, Mundigler G et al. Projected Valve Area at Normal Flow Rate Improves the Assessment of Stenosis Severity in Patients With Low-Flow, Low-Gradient Aortic Stenosis. Circulation. 2006; 113:711–721. 10. Clavel MA, Fuchs C, Burwash IG et al. Predictors of Outcomes in Low-Flow, Low-Gradient Aortic Stenosis: Results of the Multicenter TOPAS Study. Circulation. 2008; 118:S234–S242. 11. Tribouilloy C, Lévy F, Rusinaru D et al. Outcome After Aortic ValveReplacement for Low-Flow/Low-Gradient Aortic Stenosis Without Contractile Reserve on Dobutamine Stress Echocardiography. J Am Coll Cardiol. 2009; 53:1865–1873.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				12. Fougeres E, Tribouilloy C, Monchi M et al. Outcomes of pseudo-severe aortic stenosis under conservative treatment. Eur Heart J. 2012; 33:2426–2433. 13. Ribeiro HB, Lerakis S, Gilard M et al. Transcatheter Aortic Valve Replacement in Patients With Low-Flow, Low-Gradient Aortic Stenosis. J Am Coll Cardiol. 2018; 71:1297–1308. 14. Maes F, Lerakis S, Barbosa Ribeiro H et al. Outcomes From Transcatheter Aortic Valve Replacement in Patients With Low-Flow, Low-Gradient Aortic Stenosis and Left Ventricular Ejection Fraction Less Than 30%: A Substudy From the TOPAS-TAVI Registry. JAMA Cardiol. 2019; 4:64–70. 15. Sato K, Sankaramangalam K, Kandregula K et al. Contemporary Outcomes in Low-Gradient Aortic Stenosis PatientsWho Underwent Dobutamine Stress Echocardiography. J Am Heart Assoc. 2019;:1–19. 16. Kellermair J, Saeed S, Chambers JB et al. Predictors of true-severe classical low-flow low-gradient aortic stenosis at resting echocardiography. Int. J. Cardiol. 2021;:1–8. 17. deFilippi CR, Willett DL, Brickner ME et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. Am J Cardiol. 1995; 75:191–194. 18. Chahal NS, Drakopoulou M, Gonzalez-Gonzalez AM et al. Resting Aortic Valve Area at Normal Transaortic Flow Rate Reflects True Valve Area in Suspected Low-Gradient Severe Aortic Stenosis. JACC Cardiovasc Imaging. 2015; 8:1133–1139. 19. Baumgartner H, Falk V, Bax JJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				20. Otto CM, Nishimura R, Bonow RO et al. 2020 ACC/AHA Guideline for theManagement of Patients WithValvular Heart Disease. J Am Coll Cardiol. 2020;:1–173. 6-8 21. Nishimura RA, Grantham JA, Connolly HM et al. Low-Output, Low-Gradient Aortic Stenosis in Patients With Depressed Left Ventricular Systolic Function. Circulation. 2002; 106:809–813. 22. Marie-Annick Clavel. Burwash IG, Mundigler G et al. Validation of Conventional and Simplified Methods to Calculate Projected Valve Area at Normal Flow Rate in Patients With Low Flow, Low Gradient Aortic Stenosis: The Multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) Study. J Am Soc Echocardiogr. 2010; 23:380–386. 23. Hayek S, Pibarot P, Harzand A et al. Dobutamine stress echocardiography for risk stratification of patients with low-gradient severe aortic stenosis undergoing TAVR. JACC Cardiovasc Imaging. 2015; 8:380–382.	
British Society of Endocardiography	Guideline	009	012	The BSE does not currently recommend the use of indexed linear dimensions but does recommend the use of indexed ventricular volume [1, 2]. 1. *Harkness A, Ring L, Augustine DX, Oxborough D, Robinson S and Sharma V. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice. A Guideline from the British Society of Echocardiography. Echo Research and Practise (2020), 24; 7 (1): G1-G18.* 2. *Kou s et al. Echocardiographic reference ranges for normal cardiac chamber size: Results from the NORRE Study. European Heart Journal Cardiovascular Imaging (2014), 15 (6): 680-690.*	Thank you for your comment. Unfortunately, no evidence was found for the use of indexed ventricular volume in aortic regurgitation and due to the variation in current clinical practice the guideline committee were unable to make a consensus recommendation. Ventricular volume was not included in the research recommendation as the committee prioritised those factors that were

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					most likely to make a difference in outcome.
British Society of Endocardiography	Guideline	010	006	The BSE believe that the recommendation to consider surgical referral in those with severe asymptomatic mitral regurgitation and who develop a systolic pulmonary artery pressure of greater than 60 mmHg is not supported by robust evidence and lacks context. The lead author of both articles reviewed as part of this NICE recommendation is documented as Magne, with publications in 2010 (ref 155) and 2015 (ref 152). The population source is described as 'Consecutive patients matching inclusion criteria between September 2005 and September 2009 at university hospital in Belgium' for the 2010 publication, and 'Consecutive patients prospectively included between July 2007 and August 2012 across three centres in Belgium, France and Canada' for the 2015 publication. It is therefore possible, or even likely, that some patients collected in the Belgian centre between 2007 and 2009 would be presented in both publications. It is therefore inappropriate to consider these as two entirely separate research processes that have come to a similar conclusion. Furthermore, although both papers have suggested exercise PH as being associated with the development of symptoms and worse post-operative outcomes, given that exercise PH and exercise non-PH is fairly evenly split across both investigations (the 2010 paper describes that 54% of patients with moderate or severe MR did not develop exercise PH while only 46% did, the 2015 paper describes 58% of severe MR patients developing exercise PH while 42% did not), these publications have not identified severe MR as a cause of exercise PH and ultimately outcomes, merely that an SPAP of >60 mmHg is associated with symptoms of dyspnoea and	Thank you for your comment. Regarding the population source in the 2 articles, we acknowledge the possibility of these studies including overlapping cohorts. However, as they report different outcomes, one in a medically managed population and one after surgery, we do not believe it to be inappropriate to include both. They have not been pooled in any analyses, so formal double counting has not occurred. Additionally, the proportion from the Belgian centre in the later study was 35%, so this represents the maximum amount of overlap. A comment on this possible limitation has nevertheless been added to the discussion of evidence review E to highlight that these are likely to be related cohorts. Nevertheless, despite the limited evidence that in severe mitral regurgitation intervening before symptoms develop results in better outcomes, the committee agreed that

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				worse long-term outcomes in these populations. Without age-gender matched normal controls to assess response of SPAP to exercise (which we know is also influenced by PVR and flow and can therefore be seen in normal individuals with reduced pulmonary vascular compliance or significantly increased cardiac output1), it is not possible to identify exercise PH as a prognosticating factor in those with severe MR on the basis of these studies. This guidance for exercise PH in severe asymptomatic MR makes no distinction between primary and secondary MR. Given that secondary MR is often associated with intrinsic left ventricular disease (itself associated with exercise increases in left atrial pressure and consequently SPAP), the BSE would not recommend referral for intervention on the basis of exercise induced PH in those with MR secondary to LV disease2. 1. Lau EM, Humbert M, Celermajer DS. Early detection of pulmonary arterial hypertension. Nat Rev Cardiol. 2015;12(3):143-55. Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal 38 (36): 2739-2791.	it is appropriate to consider referral in those with an increase in pulmonary artery pressure to >60 mmHg on exercise testing. This was based not only on the limited evidence but also on the experience and expertise of the committee. Secondary mitral regurgitation was excluded from the review protocol for the asymptomatic group (see appendix A evidence review E) and we added 'primary' to recommendation 1.3.8.
British Society of Echocardiography	Guideline	010	006	The BSE recommend the consideration of MR proportionality when considering the likelihood of improved post-surgical outcomes in those with severe secondary MR. Patients with secondary MR represent a heterogenous group where MR may be the consequence of either extensive distortions of the MV anatomy secondary to global LV dilation and dysfunction, or due to partial distortion of the MV secondary to regional abnormalities of LV geometry and function, usually the result of regional ischaemia.	Thank you for your comment. EROA/LVEDV ratio (proportionality) in secondary mitral regurgitation was not included as a prognostic factor in the review protocol (see appendix A evidence review D) and the committee were therefore unable to make a recommendation or research

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				However, considering the degree of MR (volume or EROA) in the context of the degree of LV remodelling provides useful insight into the haemodynamic significance of MR and its contribution to LV dilatation. When the LV is severely dilated and with severely impaired systolic function, a large EROA and RF reflect a degree of secondary MR that is proportionate to the degree of LV dilation and can respond to medical therapy and interventions that aim to reduce LV EDV[1]. However, when the degree of LV dilatation is less severe, the same large EROA and RF indicate a degree of MR that is disproportionate to the degree of LV dilatation alone. These patients appear to benefit from valvular interventions to reduce MR severity rather than therapy that aim to reduce LV size alone. The concept of proportionality therefore identifies the haemodynamic consequence of secondary MR and its contribution to LV EDV, and therefore identifies those who likely to experience post-interventional remodelling and improved patient outcomes, an EROA:LVEDV ratio of 0.14 differentiating between those in whom medical therapy should be optimised and those who may be considered for transcatheter therapy. This concept of MR proportionality is further supported when considering the findings from two randomized control trials (COAPT and Mitra-FR[2,3]) which sought to assess the efficacy and safety of MitraClip in those with systolic heart failure (HF) and severe secondary MR. Although both studies randomised patients with severe secondary MR and LV dilatation with severe impairment to either medical optimisation AND MitraClip or medical optimisation alone, the outcome for each study was significantly different.	recommendation. We look forward to further research evidence in the future and can take this into account in the next iteration of the guidelines. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. The studies by Gaasch and Grayburn were not included in the evidence review as they did not meet the review protocol criteria (see appendix A evidence review D). COAPT and Mitra-FR were included in the evidence review H. The reference from Pibarot was not included as data from the two trials is reports on was already included.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The authors of the Mitra-FR study reported no difference between the MitraClip vs no MitraClip groups in rates of death from any cause or hospitalisation for HF at one-year (54.6% vs 51.3%), mortality (24.3% vs 22.4%) or rate of unplanned hospitalisation for HF (48.7% vs 47.4%). The authors concluded that although MitraClip is effective at reducing the degree of secondary MR, it does not improve prognosis in this group. However, the authors of the COAPT study reported annualised rate of hospitalisation for HF of 35.8% and death from any cause at two-years of 29.1% for the MitraClip group vs 67.9% and 46.1% respectively for the no MitraClip group. The authors concluded that among HF patients with moderate to severe MR and who remained symptomatic despite optimisation of medications, MitraClip reduces rates of hospitalisation for HF and all-cause mortality at two-years. As previously, these patients are likely to benefit from interventions that reduce MR volume. However, because the MitraClip patients within the Mitra-FR trial had a lower RV:EDV ratio, the MR contribution to LV dilatation was minimal. The potential for post MitraClip LV remodelling in this group is therefore minimal and explains why outcomes in this group were similar to those of the control group. This concept of MR:EDV proportionality is further supported by the findings of Uretsky and colleagues who found that the MRI measured post-operative reduction in LV EDV correlated very closely with the pre-operative estimate of MR volume[4]. 1. *Gaasch, W.H., Meyer, T.E. 2018. Secondary mitral regurgitation (part 1): volumetric quantification and analysis. Heart. 104:634-638*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. *Pibarot P, Delgado V, and Bax J (2018). MITRA-FR vs COAPT: lessons from two trial with diametrically opposed results. European Heart Journal - Cardiovascular Imaging (2019) 20, 620–624* 3. *Grayburn, P.A., Sannino, A., Packer, M. 2019. Proportionate and Disproportionate Functional Mitral Regurgitation: A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials. JACC: Cardiovascular Imaging. Volume 12, Issue 2, pages 353 - 362Uretsky S, Gillam L, Lang R, Chaudhury F, Argulian E, Supariwala A, Gurram S, Kain J, Subero M, Jang J, Cohen R, Wollf, S. Discordance Between Echocardiography and MRI in the Assessment of Mitral Regurgitation Severity. J Am Coll Cardiol 2015;65:1078–88*	
British Society of Endocardiography	Guideline	010	014 - 018	Recommendations for routine exercise echocardiography in asymptomatic severe MR should be made here. The statement 'base the frequency of review, within the 6-12 month timeframe, on echo findings and discussion with patient' is confusing. These patients have severe MR but normal LV size, LVEF and SPAP <50 mmHg (as intervention is not currently needed). What are the echocardiogram findings that would differentiate between patients being seen in either 6 or 12 months? ESC guidance recommends follow-up every six months by both echocardiography and clinical review in those with severe primary MR (1).	Thank you for your comment. The review question did not look at the role of routine exercise echocardiography in asymptomatic severe MR but rather indications for intervention and we therefore could not make a recommendation. The absence of a recommendation does not preclude a cardiologist from performing exercise echocardiography.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal 38 (36): 2739-2791.	Clinical practice regarding the frequency of follow up is highly variable and the committee were unable to be more specific but identified the factors that should be considered. These include how stable the patient has been over previous years, how confident you are about the patient degree of symptoms, and how close the echocardiographic parameters are to the thresholds that might indicate intervention. There is a wide range of variety in this, which is why a flexible approach as judged by the treating cardiologist and the patient is recommended.
British Society of Endocardiography	Guideline	012	014	This guidance should recommend stress-echo for asymptomatic MS (1). 1. Baumgartner H et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal 38 (36): 2739-2791.	Thank you for your comment. No evidence was identified that met the review protocol criteria for asymptomatic mitral stenosis (see appendix A evidence review H). Due to the current variation in practice and potential resource impact the committee were unable to make a recommendation. The committee agreed that this population is very

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					small and this area was not prioritised for a research recommendation.
British Society of Echocardiography	Guideline	020	021	Although this guideline states concerns regarding the reproducibility of GLS, there is already a substantial body of evidence behind the application of strain in AS, with single centre experience of over 10 years, culminating in a large patient-level meta-analysis of more than 1000 patients[1-5]. Whilst we acknowledge that values of GLS may vary between different vendors, the strength of GLS lies in serial assessment of individual patients undergoing follow-up, in which case inter-vendor variability is moot. Importantly, serial assessment of GLS is now performed routinely in the cardio-oncology setting and provides a gold-standard for identifying early cardio-toxicity prior to reduction in LVEF, which occurs later in the process[6]. Similarly, GLS is important for relative changes in strain and lends itself to the serial assessment and early detection of LV function impairment in those with significant AS. Accordingly, GLS has been shown to provide independent and additional prognostic information to conventional assessment of LV systolic function, and values of GLS >-14% have clear association with poor cardiovascular survival (irrespective of vendor), even in individuals with an LVEF≥60%[5]. The BSE suggests that this guideline should re-consider its recommendation regarding GLS in AS and add to the main document. The BSE now recommends use of GLS in the assessment of AS in our recently published AS guideline[7]. *1. Ng ACT, Delgado V, Bertini M et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J. 2011; 32:1542–1550.*	Thank you for your comment. The committee agreed that the level of evidence was not strong enough to indicate that GLS was a reliable and robust enough indicator to be used as an indication for surgery. They noted there is only a small difference in average GLS values between patients with good outcomes and those that do badly (implying intervention should be performed earlier), with considerable overlap in the range of values between the groups. We have checked the references provided and these were either included or excluded for not meeting the protocol criteria (see appendix A of evidence review D). Two studies reference the BSE guideline or a publication about the guideline. Magne was included (Dahl and Kearney were included in Magne (IPD)), Ng ACT 2011 is not a prognostic study and Ng ACT 2017/2018 had greater than 50% of patients who were symptomatic.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. Kearney LG, Lu K, Ord M et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2012; 13:827–833. *3. Dahl JS, Videbaek L, Poulsen MK et al. Global strain in severe aortic valve stenosis: relation to clinical outcome after aortic valve replacement. Circ Cardiovasc Imaging 2012;5:613–620.* *4. Ng ACT, Prihadi EA, Antoni ML et al. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. Eur Heart J Cardiovasc Imaging. 2017; 19:859–867.* *5. Magne J, Cosyns B, Popescu BA et al. Distribution and Prognostic Significance of Left Ventricular Global Longitudinal Strain in Asymptomatic Significant Aortic Stenosis: An Individual Participant Data Meta-Analysis. JACC Cardiovasc Imaging. 2019; 12:84–92.* *6. Dobson R, Ghosh AK, Ky B et al. BSE and BCOS Guideline for the TTE assessment of adult cancer patients receiving anthracyclines and or trastuzumab. (2021). JACC Cardio-Oncology 3 (1): 1-16.* *7. Ring L, Shah B, Bhattacharrya S et al. Echocardiographic assessment of aortic stenosis: a practical guideline from the British Society of Echocardiography. Echo Research and Practice. 2021; March 1.*	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Society of Endocardiography	Not included in current guideline			The main guideline, in its current form, does not mention the diagnosis, monitoring and intervention with respect to either the tricuspid or pulmonic valves. There are clinical scenarios whereby the echocardiographic assessment of these valves is important and the omission from these guidelines does not encourage sonographers or clinical teams to pro-actively manage this cohort of patients. We have published guidance with respect to the echocardiographic assessment of tricuspid and pulmonary valve disease and these should be considered for inclusion in the main guideline (1). 1. Zaidi A, Oxborough D, Augustine DX, Bedair R, Harkness A, Rana B, Robinson S and Badano LP. Echocardiographic assessment of the tricuspid and pulmonary valves: A practical guideline from the British Society of Echocardiography (2020). Echo Research and Practice 7 (4): G95-G122.	Thank you for your comment. The diagnosis and management of pulmonic valves was outside of the scope of this guideline. The diagnosis and monitoring of tricuspid valves are covered by the existing recommendations in on referral for echocardiography and monitoring. The committee has now made recommendations on interventions for tricuspid valves (1.5.15 and 1.5.16).
British Society of Endocardiography	Not included in current guideline			The BSE promote safe practise for echocardiographers across the United Kingdom and beyond, for the safety of our patients. We recommend that NICE include a comment under each of the main sub-types of valve disease that refers the reader to the current and most appropriate BSE guideline for the echocardiographic assessment of that particular pathology. This will promote safe and standardised practise across the United Kingdom. 1. Zaidi A, Oxborough D, Augustine DX, Bedair R, Harkness A, Rana B, Robinson S and Badano LP. Echocardiographic assessment of the tricuspid and pulmonary valves: A practical guideline from the British	Thank you for your comment. We did not review the appropriate echocardiographic assessment only echocardiographic parameters in relation to the intervention. We have therefore not cross-referenced the guideline you refer to. However, we do link to the BSE guideline for echocardiographic assessment in the section on 'terms used in this guideline', in reference to the definition for severe valve disease.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Society of Echocardiography (2020). Echo Research and Practice 7 (4): G95-G122. 2. Ring L, Shah B, Bhattacharrya S et al. Echocardiographic assessment of aortic stenosis: a practical guideline from the British Society of Echocardiography. Echo Research and Practice. 2021; March 1. 3. Zaidi A, Oxborough D, Augustine DX, Bedair R, Harkness A, Rana B, Robinson S and Badano LP. Echocardiographic assessment of the tricuspid and pulmonary valves: A practical guideline from the British Society of Echocardiography (2020). Echo Research and Practice 7 (4): G95-G122.	
Cardiovascular Care Partnership UK	Economic report general			Nevertheless we recognise that this is a high cost procedure and there should be a correlation between cost and benefit. Given that patient benefit should be the prime driver in assessing treatments it follows that in an evolving situation a rigorous approach to driving down costs shoulde precede any assessment of the value of the treatment and potential restriction of practice. We have highlighted one issue but would also question the effectiveness of procurement of TAVI devices, knowing thet the NHS has not always been seen as an exemplar of highly effective procurement. Do we know whether all our hospitals are performing in line with high levels of efficiency in this field? Surely this should be factored into any review process before considering restriction of access to treatment.	Thank you for your comment. 80% of all TAVI valves in the market are purchased through the NHSE High Cost Tariff Excluded Devices programme managed by the HST/NHS Supply Chain at an average price of £17,500. All manufactures are available to all trusts whether they transact through NHSSC or not. It is likely that trusts purchasing valves outside the Supply Chain programme but directly from the manufacturers are charged a different price, possibly higher than £17,500. However, it is possible that more trusts will join the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					programme in the future making the whole process more efficient.
Cardiovascular Care Partnership UK	General			We see TAVI as a highly beneficial advance in care of patients with valve disease. Indeed, some of us are involved in research into the development of other solutions to heart valve disease and regard curtailment of TAVIs as likely to have a negative effect on research and developmentinto artificial heart valves generally and possibly other approaches. You will be aware of the international cooperation in such research. TAVI itself is an evolving treatment, which is reflected in your stated 6 day stay in hospital with 2 days in ICU, quoted in the paper, no longer reflecting hospital practice, which commonly brings TAVI down to an overnight stay. Whilst hospitals may perform at different levels we believe it is incumbent on NICE, when reviewing a relatively new procedure to ascertain current development of the treatment before issuing a consultation document. Our information raises fundamental Questions about the accuracy of the data you are using, which could mislead potential respondents.	Thank you for your comment. We are aware that TAVI technology is rapidly developing, and we have revised the model to account for the recent improvement. Treatment effects are now derived by recent trials on 2nd and 3rd generation valves only and other important and ICU and LOS data are now taken from an UK study on low-risk people to better reflect contemporary NHS practice. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Cardiovascular Care Partnership UK	Guideline	011		The main driver of TAVI is patient choice for obvious reasons. It has been seen to be very effective, especially for more vulnerable patients, as is implicitly recognised in your paper. We recall that initially TAVI was the solution for patients unable to undergo a sternotomy and that seems to be behind the thinking in the paper. However, we see that only as a simple contrast beween mortality and survival, with mortality statistics usually concentrating on 30-day survival. What the statistics do not do is measure the longer term duration and quality of life, which are very important factors in this debate. We have seen examples of patients, seen as fit enough to undergo a sternotomy, but never the same afterwards because the ongoing impact of such a major operation is never measured but is often profound on subsequent quality and length of life. The impact of a restriction in practice that would deny TAVIs to patients judged to be appropriate for the treatment would place cardiologists in a compromising position when discussing patient choice and leave patients making a choice without being fully aware of the facts. That seems to undermine the whole basis of patient choice. Therefore, we would urge you not to proceed on the basis of the draft guidelines, which we see as potentially going too far in prioritising cost over patient benefit.	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Outcomes such as mortality and quality of life were extracted at the longest possible follow-up for each study and not limited to 30 days, with data up to 6 years depending on the study and outcome. Recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).
Cardiovascular Care Partnership UK	Guideline	General	General	Cardiovascular Care Partnership (UK) is the patient affiliate of the British Cardiovascular Society. This submission is made with the full support of our Council, whose members represent a wide range of cardiac patient organisations.	Thank you for your comment.
Edwards Lifesciences	Economic model TAVI	Markov 1 year	Column BL, ED	It is unclear whether double counting has been considered in the application of hospitalisations in addition to health state costs. It is noted that some of these hospitalisations may have occurred due to complications of the procedures and therefore may be captured already in the model, for example in health state costs associated with stroke or as part of a reintervention. Additionally, the application of the RR of hospitalisation with TAVI *in addition* to the application of the RR for hospitalisation for those patients with a pacemaker may also be double counting because the increased risk with TAVI may be in part due to a higher proportion of patients requiring a pacemaker. Again, it is not clear from the report whether this has been considered.	Thank you for your comment. The double counting of hospitalisation due to the combined effect of receiving TAVI and a pacemaker has now been removed (see evidence report section 2.3.2.2 for further information) It is true that some of the hospitalisation episodes calculated from the models may be due to complications of the procedure, in particular dialysis and stroke. Though, given the small percentage of people being in these health states, this would not have a major effect on the

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>model results. Nevertheless, this issue was mentioned as one of the potential limitations of the model.</td></tr>
<tr><td>Edwards Lifesciences</td><td>Economic model TAVI</td><td>Settings&inputs</td><td>Row 28-32</td><td>
<table>
<tr><th colspan="3">Reintervention</th></tr>
<tr><td rowspan="2">TAVI</td><td>% receiving TAVI</td><td>39.00%</td></tr>
<tr><td>% receiving SAVR</td><td>61.00%</td></tr>
<tr><td rowspan="2">SAVR</td><td>% receiving TAVI</td><td>39.00%</td></tr>
<tr><td>% receiving SAVR</td><td>61.00%</td></tr>
</table>

The source of the reintervention rates for the cohort is unclear. Furthermore, the figures do not reflect current practice at all. The percentage of people receiving a SAVR reintervention after a TAVI is higher (61%) than the percentage of people receiving a TAVI reintervention (31%) after an initial TAVI intervention. In practice, a ViV TAVI reintervention is a norm after a first TAVI intervention and a SAVR after a TAVI is rare (eg. Pibarot et al.2020[16]). If we follow extant evidence, the percentage of a SAVR reintervention post a first TAVI intervention should be considerably lower than the percentage of a TAVI reintervention after a first TAVI (ViV TAVI).

Moreover, in the future it can be expected that all re-interventions are done via the transcatheter approach. We in fact also have current, strong evidence showing the superiority of TAVI ViV vs. re-do SAVR (Deharo et al.2020[26] and Tam et al.2020[43])</td><td>Thank you for your comment.
We have changed the reintervention rates using data from Pibarot 2020 reported in your table although we are aware these percentages are based on a small sample size. Nevertheless, we do not expect this to change the model results considerably.</td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Economic model TAVI	Settings& inputs	Row 157	It is unclear how the relative treatment effect of hospitalization (1.24) for the TAVI arm is calculated as it is not discussed in the economic analysis report. Furthermore, the rate of hospitalization for the TAVI arm amounts to 14.4% in the NICE model. This does not reflect at all results from the PARTNER 3 trial that reports lower hospitalization with TAVI (SAPIEN 3) at both 1 year (Hazard ratio = 0.63) and 2 years (Hazard ratio = 0.67) (Leon et al.2021[12]).	Thank you for your comment. The treatment effect of hospitalisation comes from the meta-analysis of the studies included in the clinical review. This has now been made explicit in the report. Following a discussion with the committee it has now been decided to use in the base case scenario only the trials of second and third generation valves. The studies found a higher rehospitalisation after SAVR in the first year, but a lower hospitalisation beyond year 1. Therefore, we are now using two different transition probabilities and treatment effects for the first year and subsequent years.
Edwards Lifesciences	Economic report	008	007 - 022	Methods 2.2.1 Model structure 2.2.1.1 Post-procedural consequences decision tree It is surprising that in the clinical review, 'atrial fibrillation'(AF) was identified as an important post-procedural outcome, but it has not been considered	Thank you for your comment. The committee recommended against including AF as an outcome of the model because AF developed during the procedure is only a peri-

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				for inclusion in the decision tree model nor has any reason been provided for its non-inclusion. For example, Table 45 from the Evidence Review H presents the clinical evidence relating to transcatheter repair vs standard surgical replacement and reports an RR for AF 30 days post procedure (TAVI vs standard surgery) of 0.31 [CI 0.24 to 0.41]. It is worth noting that the exclusion of AF would bias the analysis in favour of SAVR because there is clear evidence that patients with AF have a reduced quality of life (Sullivan et al. 2011)[51], an excess risk of mortality and are at higher risk of stroke amongst other complications (Odutayo et al.2016)[52]. Moreover, additional resources (scans to diagnose AF, medication, and monitoring for AF treatment) would not have been captured.	procedural event and does not have any long-lasting impact on patients' health care need, mortality, or cost. It may, though, cause short-term costs but those are considered to be already captured in the hospital stay HRG used as in the base case scenario of the revised model. So, a short-term AF cost was not explicitly applied.
Edwards Lifesciences	Economic report	012	017 - 001	Table 2: Overview of parameters and parameter distributions used in the model Model inputs 2.3.1 Summary table of model inputs 30 days decision tree baseline probabilities (TAVI) It is unclear how the 'Conversion to SAVR' transition probability of 0.02 is calculated. Is it derived from a meta-analysis of the listed 6 studies or a weighted average of relevant corresponding event rates pooled together from these studies? Furthermore, 2% seems too high if taken in context with PARTNER 3 data, which reported conversion to SAVR for only one out of the 496 patients in the TAVI arm. The corresponding rate of 0.002 (or 0.2%) is almost 10 times lower than the 2% used in the model currently. Also, using data from the TAVI UK registry (2007-2012), Ludman et al.2015[53] reports 'Emergency conversion to surgery in the catheterization	Thank you for your comment. Conversion to SAVR now is informed by the most recent NICOR audit. A much lower probability of 0.55% is now used in the model instead of the 2% previously used that was calculated from the trials. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>laboratory was required in 21 patients (0.53%)'. This additional evidence also suggests that the assumed probability of 2% in the model is too high.</td><td>for people at intermediate or low surgical risk (1.5.3).

NICE and NHSEI have published a joint implementation strategy alongside the guideline.</td></tr>
<tr><td>Edwards Lifesciences</td><td>Economic report</td><td>013</td><td>017 - 001</td><td>Table 2: Overview of parameters and parameter distributions used in the model
Model inputs
2.3.1 Summary table of model inputs
30 days decision tree baseline probabilities (SAVR)

It is unclear why the rates of different post-procedural outcomes (except for 'Mortality') are the same for the intermediate risk and the high-risk population. If we consider extant 30-days evidence with transfemoral approach from PARTNER 2A and PARTNER 1A, we see that the complication rates differ across high risk and intermediate risk patients.

<table><tr><th colspan="2">Intermediate risk</th><th colspan="2">High risk</th></tr><tr><td colspan="2">PARTNER 2A (Leon et al.2016[45])</td><td colspan="2">PARTNER 1A (Smith et al.2011[24])</td></tr><tr><td>TAVI with SAPIEN (transfemoral)</td><td>SAVR</td><td>TAVI with SAPIEN XT</td><td>SAVR</td></tr></table></td><td>Thank you for your comment.

Baseline risks for procedural outcomes are now informed by the most recent NICOR audit on TAVI (Ludman 2020). Unfortunately, the audit does not stratify by patient risk, so we were unable to give different risks to low, intermediate, and high risk patients. The exception is mortality, that could be stratified by surgical risk as using the latest NACSA surgery audit. The corresponding 30-day mortality rate in the TAVI arm was calculated using the treatment effect from the trial.

We have revised the economic model based on stakeholder comments and</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response

			(transfemoral)	
Stroke	**5.1%**	**6.5%**	**4.6%**	**1.4%**
Major bleeding	**6.7%**	**41.4%**	**10.9%**	**23.1%**
Pacemaker implantation	**8.1%**	**7.1%**	**4.6%**	**4.2%**
Vascular complication	**8.5%**	**3.9%**	**14.2%**	**3.2%**
Dialysis	**0.5%**	**3.0%**	**3.4%**	**3.2%**

Similarly, 30-days evidence with SAPIEN 3 also highlight different complication rates between intermediate and high-risk patients.

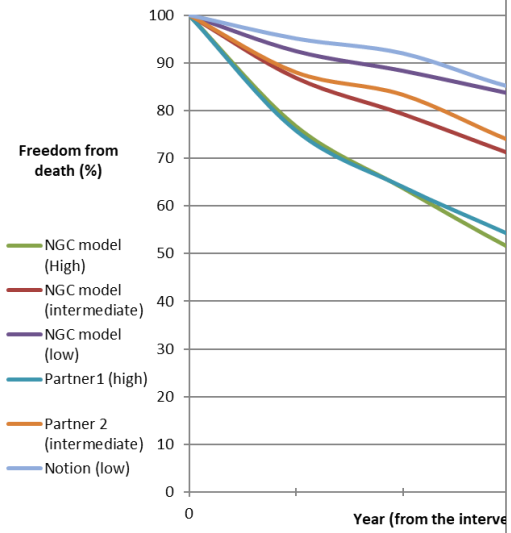
	Intermediate risk	**High risk**
	Thourani et al.2016[34]	Kodali et al.2016[4]
	TAVI with SAPIEN 3	TAVI with SAPIEN 3
Stroke	**2.5%**	**2.0%**
Major bleeding	**3.6%**	**12.3%**
Pacemaker implantation	**10.5%**	**13.5%**
Vascular complication	**6.4%**	**5.5%**

have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Mortality in the long-term is also risk specific, as a confounder-adjusted hazard ratio is applied to the mortality of intermediate risk patients described in Martin 2017 to estimate the baseline survival curves of the other risk groups (see the figure):

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Dialysis | | **0.8%** 	
Edwards Lifesciences	Economic report	013	017 - 001	Table 2: Overview of parameters and parameter distributions used in the model Model inputs 2.3.1 Summary table of model inputs 30 days decision tree baseline probabilities (SAVR) Here 6 studies are referenced for the calculation of the event baseline probabilities. However in the HVD TAVI model.xlsm Excel file, we see in the sheet 'D5 Stratification' that only 4 studies (2 high risk: Adams et al.2014[44], Smith et al.2011[24] ; 2 intermediate risk: Leon et al.2016[45],	Thank you for your comment. We revised the model to use the NICOR audit on TAVI for baseline probabilities instead of the trials included in the clinical review, so sheet D5 is not used anymore. We have revised the economic model based on stakeholder comments and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Reardon et al.2017[46]) were used to calculate the transition probabilities for all the events except 'Dialysis'(only Smith et al.2011[24] was used to inform the dialysis event rates for the SAVR arm).	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Economic report	014	017 - 001	Table 2: Overview of parameters and parameter distributions used in the model Model inputs 2.3.1 Summary table of model inputs Markov model transition probabilities Rehospitalisation It is unclear how the 'Rehospitalization' transition probability of 0.12 is calculated or derived from. Is it derived from a meta-analysis of the listed 6 studies or a weighted average of relevant corresponding event rates pooled together from these studies?	Thank you for your comment. The rehospitalisation transition probability was derived using a weighted average of the corresponding event rates from the pooled trials included in the clinical review. In addition, we recognized that rehospitalisation rate highly differs between the first and the second year after the intervention, hence we are now using two different baseline transition probabilities as well as two different relative treatment effects. This has been made explicit in the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					report (see chapter 2.3.2.2 and 2.3.3.3 of the economic report). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Economic report	016	017 - 001	Table 2: Overview of parameters and parameter distributions used in the model Model inputs 2.3.1 Summary table of model inputs Costs TAVI ICU, SAVR ICU; TAVI Total LoS, SAVR Total LoS For the TAVI and SAVR arms, ICU LoS as well as total LoS are taken from US based studies. It would have been more accurate to obtain the LoS from a UK based study. Recent data from the UK TAVI trial presented in	Thank you for your comment. The committee discussed the opportunity of using UK TAVI trial. They agreed that, although unpublished, it provided important data on ICU and hospital LOS that reflect current UK practice. Therefore, ICU and hospital LOS in the low risk population of the model reflect this

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				ACC 2020[54] indicates a median LoS of 3 days for TAVI and 8 days for SAVR.	trial. ICU and hospital LOS for higher risk groups were calculated by combining the trial data with an analysis of predictors of hospital resource use by Reinhoul (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/).
Edwards Lifesciences	Economic report	017	004-007	2.3.2 Baseline probabilities 'Baseline risks for intermediate- and high-risk patients were pooled together using data from the control arm of the papers included in the clinical review, with the exception of mortality at 30 days which uses different values for high and intermediate risk people'. It is unclear as to why all the four studies corresponding to different risk groups (High risk: Adams et al.2014[44], Smith et al.2011[24] ; Intermediate risk: Leon et al.2016[45], Reardon et al.2017[46]) are pooled together to calculate the baseline probabilities for the SAVR arm. Extant evidence shows that post-procedural outcomes vary not only across risk groups but also across device generations and access routes. This calls to question the choice of pooling the different RCTs together to derive the probabilities. Furthermore, no justification is provided for the choice of applying the same transition probabilities across intermediate and high-risk groups for all events except for mortality. The large heterogeneity considered does not allow the model to reflect what would be the TAVI cost-effectiveness from current practice	Thank you for your comment. Baseline risks now are informed by NICOR audit 2019-2020. Unfortunately, TAVI outcomes are not stratified by risk, therefore we were unable to use different probabilities for low-, intermediate and high-risk patients. Mortality is informed by NACSA AVR audit which used a risk stratification, therefore 30-days mortality will vary across risk groups. Following further committee discussion, it was agreed to use in the base case scenario relative treatment effects estimated from trials evaluating only 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to account for efficiency

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				perspective. Given the technological advancements and procedural improvements in TAVI over the past decade, we believe it is important to assess study outcomes in the context of the devices used and the study period. In this regard, we believe that 3 dimensions should not be pooled but looked at separately: 1. **TAVI major improvements with latest generation of devices** There is a large body of evidence demonstrating the improvements of outcomes with the valve's generation. A recent meta-analysis published in NATURE Scientific Research (Winter et al.2020[2]) addressed "**TAVR with contemporary next generation devices has led to an impressive improvement in TAVR safety** driven by refined case selection, improved procedural techniques and increased site experience." We are concerned that **most of the evidence used is not based on the latest technology currently in use in the UK**. An example is SAPIEN 3 balloon expandable valve, which was launched in 2014 already; only one RCT (PARTNER 3 trial) has been considered (low-risk patients using transfemoral approach) within this draft guidance. We believe a 2021 Guidance on HVD should reflect current practice and shall not be influenced negatively by first-generation technology and/or evidence that would not reflect current practice. 2. **Transfemoral Approach representing nowadays 95%+ of all TAVI interventions.** Transfemoral approach is the preferred approach and is also a critical criteria in the latest guidelines favouring TAVI vs. surgery.	improvement. These trials are predominantly on transfemoral TAVI. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Early trials were mixing transfemoral with other type of approach (transapical, subclavian, transthoracic, etc.). In the Siontis 2019 meta-analysis, we clearly see the difference between the 2 approaches as: • Transfemoral favouring TAVI: pooled HR = 0.83 with 95% CI [0.72 – 0.94] • Transthoracic favouring Surgery (not statistically significant thought): pooled HR = 1.17 with 95% CI [0.88 – 1.55] Another example is our PARTNER 3 trial for low-risk patients: only transfemoral access route was used as if not feasible it was an exclusion criteria. 3. **Different type of TAVI (balloon vs. self-expandable)** We would also like to stress that there are **important differences** for certain outcomes **between balloon-expandable valves** (SAPIEN family) and **self-expandable valves** (CoreValve Evolut, Portico, Accurate NEO, etc.). The best example is the risk of permanent pacemaker implantation – which differ dramatically between the 2 type of TAVI device[ix,xxiv,xxv,xxvi,xxvii,xxviii,xxix,xxx] (see comments below)	
Edwards Lifesciences	Economic report	022	004	2.3.3 Relative treatment effects The same mortality treatment effect of 0.91 is used for the high risk and the intermediate risk groups in the first cycle of the TAVI arm. This risk ratio is derived from a meta-analysis of 6 studies (High risk: Adams et al.2014[44], Smith et al.2011[24]; Intermediate risk: Leon et al.2016[45], Reardon et al.2017[46]). It is unclear why this approach was chosen for the TAVI arm as	Thank you for your comment. The committee decided against using risk-specific relative treatment effects for any parameter used as they thought that it was more important to capture the impact caused by the improvement of new generation valves. Hence, old trials were dropped

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				opposed to calculating indication specific risk ratios for mortality as was done for the SAVR arm. Most importantly, this does not reflect current practice. In the PARTNER 3 trial for low-risk patients treated with SAPIEN 3, the treatment effect for all-cause mortality at 1 year is 0.41. See also comments #38 and #48 above regarding the treatment effect estimates for HR and IR.	in favour of recent trials on new valves, but this made it impossible to use risk-specific rates as recent trials are mostly on low-risk patients and none on high-risk patients.This means that the same treatment effects are applied to the baseline risks regardless of the risk group (both for TAVI and SAVR). The base case scenario of the model is now using only trials of 2nd and 3rd generation valves so PARTNER 3 is included in the meta-analysis. The average treatment effect calculated from the meta-analysis is 0.93 in the first year, and 0.97 in the second year. These effects were captured in the model using 2 different calibration factors applied during the first 2 cycles of the Markov model. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Economic report	023	013 - 002	Table 7: Relative treatment effect The relative risk of pacemaker implantation (2.43) for the TAVI arm does not reflect what could be expected with balloon-expandable valves. Indeed, there are **important differences** for certain outcomes **between balloon-expandable valves** (SAPIEN family) and **self-expandable valves** (CoreValve Evolut, Portico, Accurate NEO, etc.) and the best example is the risk of permanent pacemaker implantation – which differ dramatically between the 2 type of TAVI device[ix,xxiv,xxv,xxvi,xxvii,xxviii,xxix,xxx] (see comments #28 and #39 above). Also, results from PARTNER 3 trial report one-year pacemaker implantation rates of 7.3% for the TAVI arm (vs. 5.5% for SAVR) as opposed to 15.6% used in the NICE model. The corresponding treatment effect would be 1.39. Similarly, the relative risk of vascular complications (2.45) also does not reflect results from the PARTNER 3 trial. One-year vascular complication rates for the TAVI arm correspond to 2.8% (vs. 1.5% for SAVR) in the trial	Thank you for your comment. New pacemaker implantation baseline risk in TAVI now uses the figure published by the last audit from NICOR on UK TAVI registry. This is equal to 9.7% which is similar to the rate found in PARTNER 3. The treatment effect now used in the base case scenario was calculated using only trials of 2nd and 3rd generation valves (PARTNER 3 is included). This gives a risk ratio of 1.81 (TAVI vs SAVR), which is considerably lower than the effect used in the consultation version of the model.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				while in the NICE model it corresponds to 8.6%. The corresponding treatment effect would be 1.83.	The baseline risk of vascular complication with TAVI used NICOR data as well (2.3%) and its corresponding risk ratio calculated with 2nd and 3rd generation valves only is 1.46 (TAVI vs SAVR) We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Economic report	026	021	2.3.5 Resource use and costs 2.3.5.1 Intervention costs Table 11: The cost of the intervention For TAVI intervention costs, NHS Reference Costs corresponding to 'TAVI with transfemoral approach' was used. Use of this cost reflects contemporary practice where the TF approach is used in most of the TAVI	Thank you for your comment. As the transfemoral approach has become the standard approach for TAVI, the model is focusing on TF TAVI rather than transapical or other approaches. For this reason, trials

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cases. Also, data from the UK TAVI registry indicate that the transfemoral approach was a default strategy for all patients requiring a TAVI intervention (e.g. Ludman et al.2015[53]). It is therefore unclear to us as to why, for all the other clinical inputs in the model, evidence from a mix of TAVI approaches was incorporated. A better alternative would have been to focus on a single TAVI approach (e.g. transfemoral) to maintain consistency throughout the model and reflect current practice.	looking at other approaches e.g. STACCATO were excluded from the clinical review. The base case of the now revised version of the model is taking its relative treatment effects only from trials on 2nd and 3rd generation valves. These trials are: PARTNER 2: 76.3% transfemoral PARTNER 3: 100% transfemoral Evolut: 99% transfemoral Therefore, effectiveness data are based on trials evaluating predominantly transfemoral approach TAVI. Furthermore, baseline risks are now derived from the latest NICOR TAVI audit which clearly shows that the majority of intervention are now transfemoral TAVI. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Economic report	027	001 - 005	2.3.5 Resource use and costs 2.3.5.1 Intervention costs "Regarding TAVI, it was decided to assign to the high-risk population the cost associated with an intervention with a CC higher than 8 and to the intermediate population an unweighted average of the costs associated with a CC higher and lower than 8." It would have been useful to have a justification for using unweighted rather than weighted scores for costs corresponding to the intermediate risk population.	Thank you for your comment. The committee have now decided to assign to all TAVI risk groups (low, intermediate, and high) the cost associated with a CC higher and lower than 7, therefore the weighted average is not used anymore. This is because the other HRG is likely to relate to extremely high-risk/inoperable patients. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>for people at intermediate or low surgical risk 1.5.3).

NICE and NHSEI have published a joint implementation strategy alongside the guideline.</td></tr>
<tr><td>Edwards Lifesciences</td><td>Economic report</td><td>029</td><td>019</td><td>Intermediate care and rehabilitation
Table 17: The cost of rehabilitation

The rehabilitation rates for TAVI and SAVR are obtained from Mack et al.2019[47]. This data corresponds to low risk patients. For high risk and intermediate risk patients undergoing SAVR, the rehabilitation rates can be expected to be much higher.</td><td>Thank you for your comment.

The data from PARTNER 3 do refer to low risk patients. The developers could not find a source for intermediate and high-risk patients. That may mean that the cost of SAVR is underestimated in these groups, although note that TAVI in high-risk patients is now found to be cost effective. This has now been added as a limitation in the evidence report.</td></tr>
<tr><td>Edwards Lifesciences</td><td>Economic report</td><td>042</td><td>002 - 009</td><td>Results
3.1 Base Case
<table><tr><th colspan="5">Intermediate Risk</th></tr><tr><td>Age</td><td>60</td><td>70</td><td>80</td><td>90</td></tr></table></td><td>Thank you for your comment.

The revised economic model presents results that are now more in line with the results of other recent economic analyses;</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response

ICER	£ 142 162	£ 134 874	£ 129 343	£ 136 796	
High Risk					
Age	60	70	80	90	
ICER	£ 111 487	£ 102 634	£ 97 023	£ 100 335	

The reported results from the base case are clearly not in line with extant cost-effectiveness evidence in the two tables below – which were not considered in the economic review.

Peer-reviewed Publication	Indication	Device	Country	Perspective	ICER
Pinar et al.2021 [36]	High Risk	SAPIEN 3	Spain	Spain NHS	€ 5 4
Zhou et al. 2019 [38]	Intermediate Risk	SAPIEN 3	Australia	Health care system	Dom nt
Pinar et al.2021 [36]	Intermediate Risk	SAPIEN 3	Spain	Spain NHS	€ 8 1
Zhou et al.2020 [39]	Low Risk	SAPIEN 3	Australia	3rd party payer	AUD 521

HTA	Indication	Device	Country	ICER

High risk ICER:

- NICE model: £14,000
- Tarride 2019 (Canada): £9,510 (they used a cheaper price for the TAVI valve)

Intermediate risk ICER:

- NICE model: £50,000
- Kodera 2018 (Japan): £51,210
- Tam 2018 (Canada): £43,055
- Goodall (2019) found that TAVI dominates SAVR but their analysis is using French prices for valves which are much cheaper than the ones in the UK. To give an example, a Sapien 3 valve in France is charged around £12,000 (source: https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036577833) whereas the average price of a TAVI valve in the UK is £17,500 (source: NHS Supply Chain). At this

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				HIQA | Intermediate Risk | SAPIEN XT | Ireland | Dominant HIQA | Low Risk | SAPIEN 3 | Ireland | Dominant Ontario | Low Risk | SAPIEN 3 | Canada | $ 27 196 NIPH | Low Risk | SAPIEN 3 | Norway | Dominant Furthermore, if we were to retain the same model structure but use outcomes from PARTNER 3 to populate the model, the results are completely different. In the following sections, we would like to present additional scenario analyses based on the NICE HVD model structure using the PARTNER 3 randomised controlled trial (RCT) comparing the TAVI vs SAVR in a population at low risk of surgical mortality with an anatomy allowing a transfemoral approach (Mack et al.2019[47] with 1-year data and Leon et al. 2021[12] with 2-years follow-up). Our rationale for using the PARTNER 3 trial is twofold. Firstly, we wanted to focus on our most robust evidence (RCT) that compares TAVI vs. SAVR using the SAPIEN 3 device, which is the latest generation of balloon-expandable device for TAVI – introduced into the market in early 2014 – and currently used in practice. PARTNER 3 is the only RCT available with the SAPIEN 3 balloon-expandable valve. Using SAPIEN 3 data would ensure that the results reflect the current clinical practice in the UK. The SAPIEN 3 technology has been engineered to overcome the early challenges from TAVI since its first use in 2007 by reducing catheter	price, NICE model reaches the same conclusion as Goodall • Tarride 2019: £15,500. Though they use a cheaper price for the valve as in Canada Sapien 3 is charged less (£14,500). At the same price, the revised guideline model predicts cost-effectiveness as well. Low risk ICER: • NICE model: £136,000 • Tam 2018: £15,900 but they used Canadian price for Sapien 3 (£14,500). At the same price NICE model predicts cost-effectiveness in low risk as well. We could not base the whole analysis on a single RCT because: • in the NICE reference case, meta-analysis of multiple RCTs are preferable to single RCTs • PARTNER 3 has a follow-up of 2 years only, which makes it

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				diameters, increasing the number of valves available to better reflect the patient's anatomy and by including a skirt to reduce paravalvular leaks. Historically, the first generation of the device (SAPIEN) already demonstrated superiority vs. medical treatment and non-inferiority vs. surgery for the high-risk patients (PARTNER 1B and 1A trials respectively). Whereas the 2nd generation of the balloon-expandable valve (SAPIEN XT) showed non-inferiority vs. surgery for the intermediate risk patients (PARTNER 2A). In the transfemoral subgroup more specifically, SAPIEN XT was superior vs. surgery. Our second rationale for using PARTNER 3 outcomes was to obtain unbiased results by focusing on a specific TAVI valve type (balloon-expandable which represents the majority of TAVI used in the UK), latest generation (SAPIEN 3) and with the preferred and less invasive approach (transfemoral representing 95%+ of all TAVI cases in the UK). We strongly believe that mixing evidence from: different types of TAVI valves (i.e. balloon-expandable vs. self-expandable), various valve generations (i.e. earlier generation vs the one currently in use since 2014) and different types of approaches (i.e. transapical vs transfemoral); biases results. To circumvent this, we chose to populate the NICE model with outcomes from PARTNER 3, which compares TAVI with SAPIEN 3 (transfemoral placement) against SAVR up to 2 years follow-up and present the results of the analysis herein. In line with NICE's logic, by demonstrating the cost-effectiveness of TF TAVI with SAPIEN 3 for low-risk patients – where SAVR is performing best – the results could then be extrapolated to more severe patients (i.e.	hard to estimate costs and events in the longer term • 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.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intermediate risk and high risk) where SAVR is less effective. With the increased risk of patient's severity, we believe that 1) the difference in safety and efficacy between TAVI and SAVR will increase and 2) the differences in cost will reduce. Ultimately this will result in a more favourable ICER towards TAVI. All safety and efficacy inputs in the NICE draft guideline model were updated in line with the PARTNER 3 trial where possible. This is outlined in detail in the table below which is laid out as per Table 2 in the NICE cost-utility analysis report. Two scenarios were conducted: 1. Safety and efficacy data were updated in line with the PARTNER 3 trial and other parameters such as cost estimates, health state survival hazard ratios and utilities (other than those related to TAVI and SAVR) remain unchanged. 2. Safety and efficacy data were updated in line with scenario 1 but other parameters were also updated to reflect alternative estimates using alternative sources for a low-risk population. **This would be our reference or base case scenario.** **Scenario 1** **Inputs used in Scenario 1 vs original NICE guideline model**	The scenario proposed by Edwards Lifesciences has treatment effects not to dissimilar from the one used in the revised model, with the exception of mortality which was exceptionally low in PARTNER 3 (though mortality in the model is based on a meta-analysis including PARTNER 3). Reintervention rates in scenario 1 are similar to the reintervention rate used in the revised version of the model: 1.87 vs 1.38-1.68.

Stakeholder	Document	Page No	Line No	Comments	Developer's response

Input	Original data	Updated data	Source	Cell reference on 'Settings&inputs' sheet in NICE guideline model
Cohort settings				
Start age (male and female)	70	73	Average age in Partner 3. See table 1 in paper (Mack et al. 2019[47])	L23:L24 and Patient age setting changed to 70
% males entering the model	54%	69.3%	Proportion male in Partner 3. See table 1 in paper (Mack et al. 2019[47])	L25
30 days decision tree baseline probabilities (TAVI)				
Conversion to SAVR	2.0%	0.2%	Conversion to SAVR at 30 days Partner 3 = 1/496. See table S3, Appendix (Mack et al. 2019[47])	D38
Reintervention – TAVI following TAVI*	39%	85.7%	Partner 2A 5 year outcomes (Makkar et al. 2020[32])	L29:L32
Reintervention – SAVR following TAVI*	61%	14.3%		
Reintervention – TAVI following SAVR*	39%	16.7%		

Stakeholder	Document	Page No	Line No	Comments				Developer's response
				Reintervention – SAVR following SAVR*	61%	83.3%		
				30 days decision tree baseline probabilities (SAVR)				
				Stroke	5.4%	2.4%	Any stroke at 30 days = 11/454. Life-threatening/disabling or major bleeding at 30 days = 111/454. New permanent pacemaker (baseline pacemaker excluded) at 30 days = 18/454. Major vascular complications at 30 days = 7/454 Requirement for renal replacement at 30 days = 3/454 Death from any cause = 5/454 See table S9, Appendix, 30 days endpoints with surgery (Mack et al. 2019[47])	D42:D54
				Major bleeding	28.1%	24.5%		
				Pacemaker implantation	6.3%	4.1%		
				Vascular complications	3.0%	1.5%		
				Chronic kidney injury	2.8%	0.7%		
				Mortality	Intermediate: 2.8% High: 5.4%	1.1%		
				Markov model transition probabilities				

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments				Developer's response
				Reintervention rate after SAVR	Unchanged from NICE guideline model			
				Mild PVL TAVI	33.7%	29.4%	Mild and moderate PVL at 1 year. See figure S12 in the Appendix (Mack et al. 2019[47])	D59:D63
				Mild PVL SAVR	8.5%	2.1%		
				Moderate/severe PVL TAVI	4.6%	0.6%		
				Moderate/severe PVL SAVR	0.5%	0.5%		
				Rehospitalisation	12%	11%	Rehospitalisation at 1 year with Surgery = 49/454. See table S9, Appendix (Mack et al. 2019[47])	D99
				Pacemaker hospitalisation risk ratio	Unchanged from NICE guideline model			
				Mortality				
				General population mortality	Unchanged from NICE guideline model			
				TAVI relative survival (compared to the general population) (age <80)	1 year: 86.8% 2 year: 81.1% 3 year: 74.3%	1 year: 100% 2 year: 100% 3 year: 100%	Results from Partner 3 study indicate survival as equal or above that expected in general population norms (Mack et al. 2019[47] and Leon et al. 2021[12])	D104:D106

Stakeholder	Document	Page No	Line No	Comments				Developer's response	
				Dialysis mortality hazard ratio	Unchanged from NICE guideline model				
				Pacemaker mortality risk ratio					
				Mild PVL mortality hazard ratio					
				Moderate/severe PVL mortality hazard ratio					
				Stroke (OR)					
				Post-stroke (OR)					
				Decision tree relative treatment effects (TAVI vs SAVR)					
				Stroke risk ratio	0.91	0.25 [0.07 to 0.88]	Appendix Table S9, 30-days outcomes (Mack et al. 2019[47])	D133:D138	
				Major bleed risk ratio	0.51	0.12 [0.07 to 0.21]			
				Pacemaker implantation risk ratio	2.43	1.65 [0.92 to 2.95]			
				Vascular complication risk ratio	2.82	1.44 [0.56 to 3.73]			
				Kidney injury risk ratio	0.44	0.30 [0.03 to 2.93]			

Stakeholder	Document	Page No	Line No	Comments				Developer's response
				Mortality at 30 days risk ratio	0.88	0.37 [0.07 to 1.88]		
				Markov model relative treatment effects (TAVI vs SAVR)				
				All-cause mortality risk ratio	0.91	0.41 [0.14 to 1.17] Subsequent years – unchanged from NICE guideline model	Mack et al. 2019[47]	D144
				Reintervention odds ratio	1 year: 3.52 2-3 year: 3.55 5 year: 3.55	1 year: 1.38 2-3 year: 1 5 year: 1.68	1-year data and 2-3 year data from Partner 3 2-year outcomes (see table 2, OR calculated for year 1, and assumed 1 for year 2 to 3 based on no difference demonstrated and incidence lower in TAVI arm) (Leon et al. 2021[12]) 5-year data from Kodali TVT Connect 2020[15]	D151:D153
				Rehospitalisation*	1.24	0.65 [0.42 to 1.00]	Mack et al. 2019[47]	
				Health-related quality of life (utilities)				

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				All as per the NICE guideline model	
				Decision tree utility decrements	
				All as per the NICE guideline model	
				Markov model utility decrements	
				All as per the NICE guideline model	
				Costs (All as per the NICE guideline model except those shown below)	

TAVI ICU LoS (int risk)	2	2	Appendix Table S16 (Mack et al. 2019[47])	D74:D94
SAVR ICU LoS (int risk)	4	3		
TAVI total LoS (int risk)	6	3		
SAVR total LoS (int risk)	9	7		
% discharged to intermediate care centre TAVI	0.8%	0.81%		
% discharged to intermediate care centre SAVR	14.8%	14.79%		
% discharged with home-based rehab TAVI	2.8%	2.83%		
% discharged with home-based rehab SAVR	11.3%	11.26%		

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
*Note not in original table but in Excel sheet 'Settings&Inputs' D157

Scenario 1 Results
Running the NICE guideline model for an average age of 73 (PARTNER 3) over a 30-year time horizon with each set of inputs results in the following estimates:

Results of NICE guideline model with NICE inputs
<table>
<tr><th>Per patient results</th><th>TAVI</th><th>SAVR</th><th>In</th></tr>
<tr><td>Costs per patient</td><td>£41,883</td><td>£28,065</td><td>£</td></tr>
<tr><td>QALYs per patient</td><td>5.48</td><td>5.37</td><td>0</td></tr>
<tr><td>LYs per patient</td><td>8.24</td><td>8.14</td><td>0</td></tr>
<tr><td colspan="3">ICER (per QALY)</td><td>£</td></tr>
</table>
Results of NICE guideline model with Partner 3 inputs
<table>
<tr><th>Per patient results</th><th>TAVI</th><th>SAVR</th><th>In</th></tr>
<tr><td>Costs per patient</td><td>£36,842</td><td>£25,296</td><td>£</td></tr>
<tr><td>QALYs per patient</td><td>8.50</td><td>8.05</td><td>0</td></tr>
<tr><td>LYs per patient</td><td>13.73</td><td>13.12</td><td>0</td></tr>
<tr><td colspan="3">ICER (per QALY)</td><td>£</td></tr>
</table>
Using PARTNER 3 outcomes as model inputs, we see that TAVI with SAPIEN 3 becomes cost-effective against SAVR in low-risk patients (at a WTP threshold £30,000). These results are obtained in spite of most of the NICE guideline costs for 'Intermediate risk' patients being retained.
</td><td></td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In addition to the inputs updated for Scenario 1, we have run a 2nd scenario, more credible from our perspective that we would consider as the base case (or reference scenario). The following inputs were also updated (on top of the ones described in our 1st scenario) • Reintervention split for TAVI and SAVR updated in cells L29:L32 so all patients receive TAVI on reintervention regardless of their initial procedure. This is judged to better reflect clinical practice in the future (Tam et al. 2020[43], Deharo et al. 2020[26]). • Pacemaker mortality in cell D127 set to 1 (rather than 1.17). There appears to be conflicting evidence on whether pacemaker implantation following a TAVI procedure has an impact on mortality (Mohananey et al.2017[55], Regueiro et al. 2016[56], Ueshima et al. 2018 [57]). • Costing assumptions around use of NHS reference costs for costing the low-risk procedures. For TAVI a cost of the procedure based on CC score of 0 to 7 was used to reflect a lower risk population. For SAVR an average of CC scores 0 to 5 and 6 to 11 was used for standard procedures only, again to reflect a lower risk population. • Use of discounted price for TAVI (£17,500). This is the cost at which 80% of hospitals purchased the TAVI valve under the National Procurement Scheme. This cost is also used in the NICE model as part of a scenario analysis and is more accurate as it reflects the actual price paid for a TAVI device (including various discounts and rebates).	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>

Scenario 2 Results
Using the PARTNER 3 inputs combined with the additional changes described above, the model estimates the following results:

Results of NICE guideline model with PARTNER 3 inputs

Per patient results	TAVI	SAVR	In
Costs per patient	£33,328	£25,127	£
QALYs per patient	8.50	8.05	0
LYs per patient	13.73	13.10	0
ICER (per QALY)			**£**

The results corroborate the findings presented above: TAVI with SAPIEN 3 becomes highly cost-effective against SAVR in low-risk patients (at a WTP threshold of £20,000).

It is worth underscoring that low-risk patients are the most suitable candidates for a SAVR intervention. So we agree with your logic and that's the reason why we wanted to demonstrate that when using contemporary data reflecting current practice with latest balloon-expandable valve (SAPIEN 3) in the low-risk category of patients (where surgery is performing best), then TAVI becomes highly cost-effective. The results could then be extrapolated to more severe patients (i.e. intermediate risk and high risk) where SAVR is less effective. With the increased risk of patient's severity, we believe that 1) the difference in safety and efficacy between TAVI and SAVR will increase and 2) the differences in cost will reduce. Ultimately this will result in a more favourable ICER towards TAVI.

</td><td></td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Economic report	046	015 - 022	Discussion 4.2 Limitations and interpretation "Firstly, as the source used for extrapolating long-term mortality is based on the UK TAVI registry, mortality data refer to the population currently treated with TAVI in the UK, who are mostly patients at high and intermediate operative risk (average Society of Thoracic Surgeons Score 5.06). As a result, we excluded low operative risk patients from the model as their long-term mortality could not be modelled on the basis of the available literature. Nevertheless, it is likely that low risk patients would show costs and outcomes similar to intermediate risk patients and that the intervention would be even less cost effective in this category of people." The conclusion drawn above on low risk patients is unsubstantiated. If we populated the NICE model with PARTNER 3 outcomes, the results are contrary to the claim made above. The PARTNER 3 trial studied outcomes in low risk SAS patients treated with SAVR vs TAVI with SAPIEN 3. Indeed, use of data from the PARTNER 3 trial in the NICE model under two distinct scenarios, lead to estimated ICERS in the range of £ 18,000 to £26,000 as shown in the comment above.	Thank you for your comment. In the revised version of the model, the cost-effectiveness analysis is performed on low-risk patients as well. PARTNER 3 and Evolut findings were included in a meta-analysis of 2nd and 3rd generation valves used in the base case scenario. Other outcomes from PARTNER 3 are used in the model: utilities score for low-risk patients and discharge destination. As for the NICE reference case, the analysis was undertaken using a meta-analysis of includable RCTs. Moreover, the analysis is not limited to Sapien 3 valves or low risk patients, and therefore, it could not be based only on PARTNER 3. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Economic Report MITRAL	037 038	008 - 011 029 - 031	According to the proposed model, the target population was patients affected by severe secondary MR not suitable for surgery. Data from the OxVALVE study showed that the overall adjusted prevalence of moderate or greater MR was 3.5%: primary MR was the most common aetiology compared to secondary MR (2.3% versus 0.8%). Prevalence was strongly age dependent, rising to 7.7% in the subgroup aged 75 years and older [15]. Discussing the best way to manage the uncertainty surrounding the estimate of cost effectiveness of healthcare interventions is useful to support policy makers choices (technology adoption and budget allocation). In the NICE model the probability for TEER treatment (Mitraclip) to be cost effective is almost 50% at a threshold of £ 30,000 per QALY, compared to medical management. This probability underestimates the result presented by Shore J et al. (2020) that showed a 65% likelihood for the same therapy of being cost-effective at the same threshold and with the same comparator, when using data from the COAPT study as well. Considering the ICER of the NICE model slightly exceeds the cost effectiveness threshold of £ 30,000, we believe that the conclusion of the analysis should also consider the epidemiology of the disease (as mentioned above) and the future improvements in terms of clinical gains and procedural efficiency for this specific treatment.	Thank you for your comment. The conclusions of the model should not be affected by the prevalence of the disease, which is more relevant for a cost impact analysis. If in the future new clinical and efficiency improvements or price reductions occur then cost effectiveness can be re-assessed via NICE's surveillance process.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[15] Thomas J Cahill, Anthony Prothero, Jo Wilson et al (2021). Community prevalence, mechanisms and outcome of mitral or tricuspid regurgitation, Heart 2021;0:1–7.	
Edwards Lifesciences	Economic Report MITRAL	038	022 - 027	Even though, as assessed in the draft Guideline, the economic model developed by NICE did not find MitraClip to be cost effective for adults with secondary MR, the recent health economic analysis by Shore J *et al.* (2020) demonstrated that the TEER therapy was a cost effective intervention compared to GDMT in patients with severe secondary MR, with a higher probability of 65% of being cost effective at a threshold of £30,000 per QALY. Both analyses, although modelled and structured differently, generated very similar ICERs (they just differ by £210), giving some degree of confidence in the results of both models. Taking in consideration the assumptions and limitations when modelling and comparing different therapeutical options, both results refer to the current treatment costs and clinical outcomes in the available literature. It's very likely that procedural efficiencies of transcatheter mitral therapies will improve over time and result in future clinical gains and cost reductions, increasing the economic sustainability of such therapies.	Thank you for your comment. As mentioned, indeed the results of this analysis and Shore 2020 are very similar and show that MitraClip is on the £30,000 threshold of cost-effectiveness in the UK. Above the £20,000 threshold, an intervention is considered cost effective only if there are a number of factors as per NICE reference case (6.3.3). These factors were not found to occur for MitraClip and so the intervention was not considered cost-effective. However, if future studies will show improvement in efficiency, then cost effectiveness can be re-assessed via NICE's surveillance process. The recommendations were revised following some of the stakeholder comments to consider percutaneous edge-to-edge repair for those whose

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					medical management does not improve symptoms. This would allow for some people in the UK to have access to the MitraClip.
Edwards Lifesciences	Evidence review H – Interventions	General	General	**Excluded Evidence – Mechanical and Bioprosthetic Valves** With regards to the distinction between mechanical and bioprosthetic valves in surgical valve replacement, the clinical studies selection method excluded valuable evidence in which important and significant clinical outcomes have been reported. 1. Current and updated treatment guidelines (2020 ACC/AHA and 2017 ESC/EACTS) distinguish between mechanical and bioprosthetic valves, with the 2020 ACC/AHA Guidelines having recently lowered the age threshold and therefore do recommend bioprosthetic AVR from 70 years to 65 years (Class 2A). ESC/EACTS guidelines will be updated on August 2021. 2. While we appreciate the justification for the study selection methodology to exclude US publications, we feel it important to draw attention a recent publication on "Similar Long-term Survival after Isolated Bioprosthetic versus Mechanical Aortic Valve Replacement: A Propensity-Matched Analysis" published in the Journal of Thoracic and Cardiovascular Surgery early this year 2021 (1). This publication is of particular importance as it was used to support and inform recent U.S ACC/AHA 2020 guidelines updates. The paper specifically highlights the following key findings:	Thank you for your comment and provision of references. The comparison between mechanical and bioprosthetic valves in surgical valve replacement was not prioritised for review as a subgroup to explore in the presence of heterogeneity. No heterogeneity was found and the committee were therefore unable to make recommendations in this area.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				a. Bioprosthetic valves in the aortic position offer excellent survival to at least 18 years, similar to mechanical valves, despite reoperations for structural valve deterioration. b. Bioprosthetic AVR is a reasonable alternative for younger patients who desire to be free of anticoagulation for lifestyle or personal reasons. 3. Rodríguez-Caulo *et al* (2021) (2) conducted a large observational study in Spain with 5,215 patients, concluding that bioprostheses seem a reasonable choice for patients aged 50 to 65 years of age, particularly for those older than 55 years, because of the long-term survival and the lower-risk related especially to major bleeding compared with mechanical prostheses. 4. When it comes to distinguishing and choosing between a mechanical versus a bioprosthetic valve, we regret that following randomized controlled trial was not considered within the draft guideline as it relates to differences in prosthetic valve outcomes; most notably, bleeding events and stroke: Stassano *et al* (3) performed an RCT that included patients aged 50 to 70 years and reported results for adverse events (AEs) as percentage per patient-year, bleeding event rates were 0.72% per patient-year with bioprosthetic valves and 1.47% per patient-year with mechanical valves across a mean follow-up period of 106 months (~8.8 years). Furthermore, although only RCTs may be considered within this review, it needs to be stated that all studies types have reported that rates of major bleeding after Surgical Aortic Valve Replacement (SAVR) and Surgical Mitral Valve Replacement (SMVR) are	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				numerically lower with bioprosthetic valves than with mechanical valves, regardless of the age group. 5. Additionally, advances in tissue treatment technologies through anticalcification treatment by using stable functional group capping and preservation by glycerolization and thus being able to be stored in dry conditions, has demonstrated significant improvements in hemodynamic and anticalcification properties when compared with standard of care valves (1). These findings have been consistently demonstrated over four years follow-up, whereby no unexpected early thrombosis events or noncalcific structural valve deterioration was observed (4), in addition to which 0% structural valve degeneration has been observed over a five-year follow-up period (5). This remains of special relevance for younger and active population as well as women considering pregnancy. 6. We recognize that the evidence base for Quality of Life among patients who have received a bioprosthetic or mechanical valve is quite limited. Overall health status reported using the SF-36 questionnaire is similar among patients who have received a bioprosthetic or mechanical valve, however patients with bioprosthetic valves report lower anxiety than those with mechanical valves, particularly regarding their sexuality and partnerships. In addition, many patients with mechanical valves experience lifestyle disturbances and concerns about side effects (i.e. bleeding) associated with the need for daily anticoagulation use, as well as disturbances caused by the mechanical valve's clicking sound. Patients who have undergone SMVR with a mechanical valve, experience similar disturbances caused by their valve's clicking	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				sound as those who have undergone SAVR; specifically, patients report that the valve sounds disrupt their ability to sleep or conduct daily activities. 7. Economic evidence in which the decision between a mechanical or bioprosthetic valve were additionally not taken into consideration by the draft guidelines, due also in part to the study selection criteria methodology as defined in Section 1.5 of the draft guideline. a. Costs - Annual treatment and monitoring costs are higher with mechanical valves than with bioprosthetic valves, a finding that is largely driven by the costs of anticoagulation therapy and associated monitoring with mechanical valves. b. Length of Stay - Several studies have observed significantly shorter hospital Length of stays (LOS) for bioprosthetic valves than for mechanical valves. Bioprosthetic valves are associated with significantly shorter post-operative LOS in the recovery ward than mechanical valves. 1. Flameng W, Hermans H, Verbeken E, Meuris B. , "A randomized assessment of an advanced tissue preservation technology in the juvenile sheep model.," J Thorac Cardiovasc Surg. , Vols. ;149:340-345., 2015 2. Emiliano A. Rodriıguez-Caulo et al., "Biological versus mechanical prostheses for aortic valve replacement. SPAVALVE Study Group," The Journal of Thoracic and Cardiovascular Surgery, no. https://doi.org/10.1016/j.jtcvs.2021.01.118, 2021. 3. Stassano P, Di TL, Monaco M, Iorio F, Pepino P et al. , "Aortic valve replacement: a prospective randomized evaluation of mechanical	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				versus biological valves in patients ages 55 to 70 years.," Journal of the American College of Cardiology, Vols. 54 (20): 1862-1868., 2009. 4. Johnston DR, Griffith B, Puskas JD et al. on behalf of The COMMENCE Trial Investigator., "Intermediate-term outcomes of aortic valve replacement using a bioprosthesis with a novel tissue," J Throac Cardiovas Surg., no. doi:10.1016/j.jtcvs.2020.01.095, 2020 5. Five-Year outcomes of the COMMENCE Trial investigating aortic valve replacement with a novel tissue bioprosthesis. Presented at the Society of Thoracic Surgeons Annual Meeting, January 2021, 2021.. 6. Rodriguez-Caulo EA, Macias D, Adsuar A, Ferreiro A, Arias-Dachary J et al., "Biological or mechanical prostheses for isolated aortic valve replacement in patients aged 50-65 years: the ANDALVALVE study.," European Journal of Cardio-thoracic Surgery , Vols. 55 (6): 1160-1167., 2019	
Edwards Lifesciences	Evidence Review H: Interventions	007 - 009	006	1.3 PICO Table Table 1: PICO Characteristics of review questions Regarding the study design considered in the PICO table, we regret that the evidence review was limiting the criteria to randomized controlled trials (RCT) only. Besides, the overall evidence selection criteria and the rational for the narrow evidence profile used (i.e. RCTs only) remains unclear to us. Especially that the Committee acknowledges (page 147, lines 9-12) that "*it is well established that interventions should be performed over conservative management and the reason there are no RCTs currently is because it would*	Thank you for your comment. It was agreed to be appropriate to limit to randomised data to inform this evidence review because this allows comparison between the available treatment options and limits confounding effects. Systematic reviews of randomised controlled trials were also considered for inclusion, but none met the inclusion criteria. The

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				be unethical to include such a comparison within an RCT for the operable population". This resulted in **excluding valuable evidence relative to transfemoral SAPIEN 3™ balloon expandable valve** used in current practice[i,ii,iii,iv]. Among the many important evidence excluded, several meta-analyses based on RCT and published in peer-reviewed journals [v,vi,vii,viii,ix]. Overall, the results from these meta-analyses showed that, compared with SAVR, **TAVI is associated with a statistically significant reduction in all-cause mortality, stroke and cardiovascular death**. The use of TAVI was also associated, compared to surgery, with **reduced risk of acute kidney injury, atrial fibrillation and major haemorrhage[ix] (p<0.01 for all).** In these studies the use **of SAPIEN 3™ balloon expandable valve** was also associated with a statistically significant **improvement in the quality of life of the patients** (measured by KCCQ-OS, SF-36 physical functioning scale and the SF- 36 mental health scale) at 1 month. This significant improvement in quality of life was **maintained at 1 year[i] and at 2 years (Leon et al 2021)**[x] follow-up. The use of the latest evidence, practice and technologies, together with the use of real-world evidence, are part of NICE 2021-2026 strategy released very recently.	latest follow-up data from all included trials has now been included, including the Leon 2021 report. The sentence you refer to on page 147, lines 9-12 contained an error which has since been corrected, as it should have read 'inoperable population' not 'operable population'.
Edwards Lifesciences	Evidence Review H: Interventions	009	008 - 016	1.4 Clinical Evidence 1.4.1 Included Studies Aortic valve disease The first generations TAVI device Edwards **SAPIEN and SAPIEN XT™ are no longer used** in current practice since 2014 already. Unfortunately, the	Thank you for your comment. It was agreed to be appropriate to limit to randomised data to inform this evidence review because this allows comparison between the available treatment options and limits confounding effects, which is why the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				literature search and the RCTs included in the evidence review rely in the big majority on these initial generations of TAVI as follows: - The seven studies comparing transcatheter replacement versus standard surgery: SAPIEN (Nielsen et al 2012, Smith et al 2011) and SAPIEN XT (Leon et al 2016) - The study comparing transcatheter replacement versus pharmacological treatment: SAPIEN (Leon et al 2010) Hence **only one RCT** (Mack et al 2019) using **SAPIEN 3™, currently used in practice, was included in the evidence review.** The technical improvements are substantial between the early SAPIEN generations and **SAPIEN 3™ with a major impact on the clinical outcomes.** SAPIEN 3 ™ valve, launched in 2014, brings critical new technical features that have shown to significantly improve patients' outcomes[xi,xii] vs. the previous SAPIEN generations (SAPIEN and SAPIEN XT). The technical incremental improvements resulted also in **developing the transfemoral (TF) access route**. The latter is currently the standard practice and used in more than 95% of the cases, due to its **minimally invasive nature**, associated with shorter hospital stay and dispensing with general anaesthesia. Moreover, **additional recent studies** are available showing the differentiating benefit of **SAPIEN 3™ compared to previous SAPIEN™ generations**. In 2020 the 5-year follow-up data addressing the question of	additional studies listed in relation to SAPIEN 3™ were not eligible for inclusion in the clinical review. The revised version of the model calculates treatment effects from 2nd and 3rd generation valve only. These are predominantly assessing the transfemoral approach. In addition, the model includes a scenario analysis where reintervention treatment effect is calculated from Evolut and PARTNER 3 only, to account for the improvement of latest generation valves. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				durability and mid-term outcomes of TAVI compared with SAVR were released. • The first study was presented at the June 2020 TVT Connect conference by Pr Kodali [xiii]. A propensity-matched analysis comparing 5-year outcomes with **SAPIEN 3™** and surgery in intermediate-risk patients demonstrated**:** o Similar rates of mortality and all strokes o Lower rate of disabling stroke favouring TAVR, and lower rate of nondisabling stroke favouring surgery o Lower new pacemakers with surgery, but similar rates of endocarditis, AV re-intervention, and valve thrombosis. The authors concluded that these results with **SAPIEN 3™** demonstrating **clinical outcomes and valve durability comparable to surgery at five years**, associated with low PVR, are encouraging and continue to support TAVR as an alternative to surgery. • **The durability** question was also addressed by Pibarot et al (2020)[xiv] – using the latest VARC 3 definitions. The authors showed that the second generation of balloon-expandable valves, SAPIEN XT™, had lower midterm durability compared with surgery, whereas the third generation **SAPIEN 3™, had better durability compared with SAPIEN XT™** and was **similar to surgery**. The authors provided several explanations related to the valve technical features that result in lesser leaflet mechanical stress and thus better durability.	NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Additionally, a recent study from Blackman, et al 2019[xv] sought to evaluate the incidence of hemodynamic structural valve deterioration up **to 10 years following TAVR from the UK TAVI Registry**. The study found excellent overall long-term durability with TAVR valves. A recent multicentre study from France also confirmed promising long-term durability of TAVR valves. The study reported the **7-year** cumulative incidence of bioprosthetic valve failure (BVF) was 1.9%, and moderate and severe structural valve deterioration (SVD) was 7.0% and 4.2%, respectively. These outcomes were based on the newly published European criteria for BVF and SVD[xvi]. An observational study from Canada followed patients for 10 years after TAVI with early-generation THVs and concluded that there was **a low rate of structural valve deterioration and valve failure at 10-year follow-up** (6.5%) and a low rate of SVD/BVF (6.5%)[xvii],[xviii]. Question 1: this draft guideline based its intervention recommendations for AS on the clinical evidence of technologies that are no longer used in practice by healthcare professionals. Hence these recommendations, in our view, **do not represent the current clinical practice nor the current interventions used**. The use of the latest evidence, practice and technologies are part of NICE 2021-2026 strategy released very recently.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Considering the substantial clinical benefit **SAPIEN 3™ valve brings compared to the earlier SAPIEN devices, drawing such recommendations might put the patients' safety and health at stake.**	
Edwards Lifesciences	Evidence Review H: Interventions	012	033 - 045	1.4.2 Excluded studies As mentioned above, the selection of RCTs only for this review, resulted in **excluding valuable evidence relative to transfemoral SAPIEN 3™** used in current practice. Evidence requirements for Medical Devices have been the subject of debate for many years. We believe that the NICE should consider the evidence requirement for each question while leaving room **for flexibility and adaptability**. It is possible to obtain comparative evidence derived from sound clinical study designs with control groups, when an RCT is not possible. In the context of implantable medical devices like TAVI, this is even more relevant, considering the contextual factors (i.e., the users' proficiency or 'learning curve', training, interpretation, multiple indications, pace of the technologies' innovation cycle, the adaptation of the care pathways, health systems performance, the socio-economic and organisational efficiency impact, etc.); In the situation of SAPIEN 3™, after the enrolment of the PARTNER 2 trial (Leon et al 2016) was completed, the FDA agreed to extend the PARTNER 2 trial with **a non-randomized arm with the SAPIEN 3™** device for intermediate risk patients, using the same inclusion/exclusion criteria. The **pre-specified propensity score analysis** to compare SAPIEN 3™ with the enrolled surgical arm after one-year follow-up was agreed with the	Thank you for your comment. It was agreed to be appropriate to limit to randomised data to inform this evidence review because this allows comparison between the available treatment options and limits confounding effects, which is why the additional studies listed in relation to SAPIEN 3™ were not eligible for inclusion in the clinical review. Study designs to be included in each review were discussed with the committee during the development of each review protocol and for this review there was considered to be enough RCT evidence, with no concerns about much of this evidence being from older generation devices raised. Therefore, non-randomised studies were not prioritised for this review

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				FDA. Because of the **clinical equipoise principle**, the **trial expert team and FDA refrained from randomization**, but instead wanted to give patients access to SAPIEN 3™ in a controlled setting. Hence, regurgitation was added to the composite endpoint to raise the bar even more, demonstrating paravalvular leak improvements as a very patient relevant TAVI outcome. The **results of the SAPIEN 3™ cohort showed the superiority of the new device generation vs PARTNER 2 surgical arm (Thourani et al 2016[xix])** There are also other studies which allow us to assess the impact of technical developments of different generations of bioprostheses on clinical results. The PARTNER 1A trial and the study by Hermann et al (2016)[xx] report the results of a patient cohort at increased surgical risk treated respectively with the first (SAPIEN™) and the third (SAPIEN 3™) generations of Edwards Lifesciences bioprostheses. The study by Hermann et al. with **SAPIEN 3™, reported a lower complication rate** compared to the initial PARTNER 1A trial: Vascular complications after TAVR have been associated with mortality in all studies and were 32% at 1 year in the PARTNER 1B[xxi] study of inoperable patients, 18% in the PARTNER 1A[xxii] study of high risk (HR) patients with the first-generation SAPIEN, and 17% in PARTNER IIB[xxiii] with the SAPIEN XT **compared with <10% in the study by Hermann et al 2016 with SAPIEN 3**. The authors concluded that third-generation balloon-expandable **SAPIEN 3 THV is associated with a very low rate of early and 1-year complications and 1-year mortality in HR and inoperable patients with severe AS**. The combination of new design features of SAPIEN 3,	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				procedural improvements, operator experience, and improved patient selection has contributed to **a low rate of important adverse events (including stroke) and a high rate of 1-year survival in HR and inoperable patients** with severe AS.For patients at increased surgical risk (previously referred to as intermediate risk patients), similar conclusions can be drawn. The use of **SAPIEN 3™ (PARTNER 2A S3i cohort[i])** is associated with **a significant (p <0.001) improvement in the quality of life** (KCCQ-OS score; the SF-36 physical functioning scale and on the SF-36 mental health scale) at 1 month and 1 year compared to the previous generation of bioprosthesis - SAPIEN XT™. **Incremental developments leading to subsequent innovation like SAPIEN 3™ bioprosthesis are associated today with clinical outcomes superior to those obtained with the older generation of bioprosthesis.** Question 1: this draft guideline based its intervention recommendations for AS on the clinical evidence of technologies that are no longer used in practice by healthcare professionals. Hence these recommendations, in our view, **do not represent the current clinical practice nor the current interventions used**. Considering the substantial clinical benefit **SAPIEN 3™ valve brings compared to the earlier SAPIEN devices, drawing such recommendations might put the patients' safety and health at stake.**	
Edwards Lifesciences	Evidence Review	048	007	"*Table 3. Clinical evidence summary: Evidence not suitable for GRADE analysis*."	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	H: Interventions			The quality assessment of the "Hospital length of Stay" outcome presented in this table is extremely mis-leading for the following reasons: - It considers only 3 studies; it is unclear why only these 3 studies were used and the reason for excluding the other RCT selected for the review - The GRADE analysis not being suitable, it is unclear what was the type of analysis that was used for this specific outcome and on what basis the risk of bias (high/very high) was evaluated? We regret that the evidence review was limiting the studies selection criteria to randomized controlled trials (RCT) only. Besides, the overall evidence selection criteria and the rational for the narrow evidence profile used (i.e. RCTs only) remains unclear to us. Especially that the Committee acknowledges (page 147, lines 9-12) that "*it is well established that interventions should be performed over conservative management and the reason there are no RCTs currently is because it would be unethical to include such a comparison within an RCT for the operable population*". More specifically for the hospital length of stay measurement, the study by Thourani et al[iii] found that the median **postoperative length of hospital stay was shorter in the TAVI cohort than in the surgical cohort** (4 days *vs* 9 days) and a higher percentage of patients went home after the procedure (912 [85%] *vs* 436 [46%]).	Data for hospital length of stay was available for additional studies, but results are presented for these three studies separately as the studies reported median values, meaning they could not be pooled with other studies reporting means and standard deviations. Analysis could not be performed on these median values but they were presented to the committee alongside the data from studies where pooling was possible so all data relevant to this outcome was considered. Risk of bias for this data was assessed as for all other outcomes in the review, as described in the methods chapter, section 2.5. It was agreed to be appropriate to limit to randomised data to inform this evidence review because this allows comparison between the available treatment options and limits confounding effects. The sentence you refer to on page 147, lines 9-12 contained an error which has since been corrected, as it should have read

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The PARTNER 3 trial (Mack et al 2019) also shows a similar trend with an even more **significant difference between SAPIEN 3 and surgery (3 days in the TAVI cohort vs 7 days in the surgical cohort; p<0.001).** Question 1: The evidence reviews, by **excluding valuable evidence relative to transfemoral SAPIEN 3™ balloon expandable valve,** has overlooked an important impact of the use of **SAPIEN 3™** valve- i.e. optimize the hospital resource utilisation – by avoiding general anaesthesia and intubation, shortening (or preventing) ICU stay, and accelerating hospital discharge and recovery. This impact is even more critical in the current context of the COVID-19 pandemic and the dramatic **burden on healthcare resources and facilities.**	'inoperable population' not 'operable population'.
Edwards Lifesciences	Evidence Review H: Interventions	051 - 055	002	Table 5. Clinical Evidence Summary We do not understand the RR calculation and we would like to reiterate that most likely it includes heterogenous studies mixing TAVI valve generations and type of devices with access routes. We would like to propose to you the RR based on our latest and current SAPIEN 3 generation TAVI balloon-expandable valve with the transfemoral approach. As you will see the various relative risks are reduced considerably. • **All-cause mortality at 12m. RR = 1.07 and RR = 1.03 (time to event) are calculated**. o High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 21.3% vs. 25.2% for SAPIEN and SAVR respectively (RR = 0.85).	Thank you for your comment. The design of the review in terms of pooling and stratification were discussed at length with the committee during the development of the review protocol. It was agreed that studies comparing transcatheter intervention with surgical intervention would be combined initially, regardless of factors such as device generation and TAVI approach. However, it was agreed that for any outcomes where heterogeneity was present in the meta-analysis, the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				When using the data from SAPIEN 3 from Hermann (same inclusion / exclusion) we have a 10.7% all-cause mortality at 1 year (**RR = 0.43**) ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 10.0% vs. 12.3% for SAPIEN XT and SAVR respectively (RR = 0.81). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 6.5% all-cause mortality at 1 year (**RR = 0.53**) • **Cardiac mortality at 12m. RR = 1.12 and RR = 0.99 (time-to-event) are calculated** ○ High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 11.9% vs. 11.8% for SAPIEN and SAVR respectively (RR = 1.01). When using the data from SAPIEN 3 from Hermann (same inclusion / exclusion) we have a 6.1% cardiovascular mortality at 1 year (**RR = 0.52**) ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 6.0% vs. 9.0% for SAPIEN XT and SAVR respectively (RR = 0.75). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 4.0% cardiovascular mortality at 1 year (**RR = 0.50**) • **Intervention-related mortality at 30d. RR = 0.88 is calculated**	impact of certain factors that were thought most likely to have an effect on outcome (including access route and operative risk, for example) on the outcome would be explored using subgroup analyses. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				○ High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 3.7% vs. 8.2% for SAPIEN and SAVR respectively (RR = 0.45). When using the data from SAPIEN 3 from Kodali (same inclusion / exclusion) we have a 1.6% all-cause mortality at 30 days (**RR = 0.20**) ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 3.0% vs. 4.1% for SAPIEN XT and SAVR respectively (RR = 0.73). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 1.1% all-cause mortality at 30 days (**RR = 0.27**) • **Intervention-related stroke or TIA at 30d. RR = 0.91 is calculated** ○ High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 4.6% vs 1.4% for SAPIEN and SAVR respectively (RR = 3.29). When using the data from SAPIEN 3 from Kodali (same inclusion / exclusion) we have a 2.0% incidence of stroke/TIA at 30 days (**RR = 1.43**) ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 5.1% vs. 6.5% for SAPIEN XT and SAVR respectively	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(RR = 0.78). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 3.1% incidence of stroke/TIA at 30 days (**RR = 0.48**) • **Intervention-related major bleeding at 30d. RR = 0.51 is calculated** o High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 10.9% vs. 23.1% for SAPIEN and SAVR respectively (RR = 0.47). When using the data from SAPIEN 3 from Kodali (same inclusion / exclusion) we have a 12.3% incidence of major bleeding at 30 days (**RR = 0.53**) o Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 6.7% vs. 41.4% for SAPIEN XT and SAVR respectively (RR = 0.16). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 3.6% incidence of major bleeding at 30 days **(RR = 0.09)** • **Need for re-intervention at 12m. RR = 4.95 and RR = 3.28 (time-to-event) is calculated** o High Risk (HR) Data not available unfortunately but events were very few (also due to competing risk of mortality) o Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				have 1.1% vs. 0.6% for SAPIEN XT and SAVR respectively (**RR = 1.83**). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 0.7% incidence of a need for re-intervention at 1y (**RR = 1.17**). In our 5y data recently published by Pibarot (2020)[xiv] at 5y follow-up we didn't see any additional risk of re-intervention with SAPIEN 3 (vs. SAVR) • **Re-hospitalization at 12m. RR = 1.34 and RR = 0.94 (time-to-event) is calculated** o High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 17.5% vs. 15.2% for SAPIEN and SAVR respectively (RR = 1.15). When using the data from SAPIEN 3 from Hermann (same inclusion / exclusion) we have a 15.6% re-hospitalization rate at 1y (**RR = 1.03**) for entire cohort (data not available for transfemoral cohort only) o Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 13.1% vs. 14.8% for SAPIEN XT and SAVR respectively (RR = 0.89). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 10.5% re-hospitalization rate at 1y (**RR = 0.71**) • **Intervention-related pacemaker implantation at 30d. RR = 2.43 is calculated** o High Risk (HR)	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 4.6% vs. 4.2% for SAPIEN and SAVR respectively (**RR = 1.10**). When using the data from SAPIEN 3 from Kodali (same inclusion / exclusion) we have a 13.5% incidence of permanent pacemaker implantation at 30 days (**RR = 3.21**). ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 8.1% vs. 7.1% for SAPIEN XT and SAVR respectively (**RR = 1.14**). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 10.5% incidence of permanent pacemaker implantation at 30 days (**RR = 1.48**) • **Intervention-related AF at 30d. RR = 0.31 is calculated** ○ High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 7.5% vs. 18.6% for SAPIEN and SAVR respectively (**RR = 0.40**). ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 4.9% vs. 26.7% for SAPIEN XT and SAVR respectively (**RR = 0.18**). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 3.2% incidence of AF at 30 days (**RR = 0.12**) • **Major vascular complications at 30d. RR = 2.82 is calculated**	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				○ High Risk (HR) In our PARTNER 1A trial with our 1st generation of SAPIEN device for the transfemoral access route we have 14.2% vs 3.2% for SAPIEN and SAVR respectively (RR = 4.44). When using the data from SAPIEN 3 from Kodali (same inclusion / exclusion) we have a 5.5% incidence of major vascular complication at 30 days (**RR = 1.72**) ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 8.5% vs. 3.9% for SAPIEN XT and SAVR respectively (RR = 2.18). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 6.4% incidence of major vascular complication at 30 days (**RR = 1.64**) • **Valve endocarditis at 12m. RR = 1.29 is calculated** ○ High Risk (HR) Data not available unfortunately but events were very few (also due to competing risk of mortality) ○ Intermediate Risk (IR) In our PARTNER 2A trial with our 2nd generation of SAPIEN device (SAPIEN XT) for the transfemoral access route we have 0.8% vs. 0.9% for SAPIEN XT and SAVR respectively (RR = 0.89). When using the data from SAPIEN 3 from Thourani (same inclusion / exclusion) we have a 0.8% incidence of endocarditis at 1 year (**RR = 0.89**)	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Evidence Review H: Interventions	058	002	Table 7: Clinical evidence summary: Transcatheter replacement vs. surgery replacement (unclear/mixed invasiveness) Per the "Table 2: Summary of studies included in the evidence review" (page 14), Table 7 seems to be referring to the study by Popma et al 2019 (summary on page 21). As presented Table 2 (page 14), only one specific type of TAVI valve (i.e. self-expandable valve with subclavian access route) was used in this trial and the patient population is limited to the low surgical risk patients with SAS. We are concerned that the assessment presented in Table 7 (based on one study only) may **not be representative of the safety and efficacy all types of TAVI valves** available on the market (i.e. balloon expandable SAPIEN 3 valve) and **also of all patient groups** who could benefit from TAVI. Question 1: This evaluation is generalising the result of one type of valve to all TAVI without any consideration of: - The major technical specifics of the different valves on the market (self-expandable vs SAPIEN 3 balloon-expandable) - The access route associated with each (subclavian, transfemoral) The safety results[xxiv],[xxv],[xxvi],[xxvii],[xxviii],[xxix],[xxx]: **higher incidence of aortic regurgitation and permanent pacemaker use were reported with the self-expandable supra-annular valves** compared to balloon expandable SAPIEN 3 valve.	Thank you for your comment. The Evolut low risk trial (Popma 2019) has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Evidence Review H: Interventions	061	002	1.4.4.2 Aortic Stenosis (bicuspid) No evidence was identified for this stratum. As mentioned for the non-bicuspid sections, we regret that the evidence review was limiting the criteria to randomized controlled trials (RCT) only. The use of the latest evidence, practice and technologies, together with the use of real-world evidence, are part of NICE 2021-2026 strategy released very recently. Actually, for patients with bicuspid valve, Halim et al 2020[Error! Bookmark not defined.] bring strong evidence from real world practice. This study is the **largest analysis (cohort of 170,959 patients)** comparing TAVR for the treatment of AS in bicuspid versus tricuspid aortic valves. **The authors showed that there were no differences in one-year mortality, stroke, or major bleeding between the patients with bicuspid aortic valve and tricuspid aortic valve.** The use of **current-generation balloon-expandable valves was associated with a lower risk of significant paravalvular leak in patients with bicuspid AV than current-generation self-expanding valves.** The authors concluded that *"TAVI is a viable treatment option for patients with bicuspid AV disease"*. With the current-generation valves (**SAPIEN 3 balloon expandable valve** was used in 73.4% of the TAVR procedures performed in patients with bicuspid aortic valve), **TAVR is both safe and effective for the treatment of bicuspid aortic valve stenosis.**	Thank you for your comment. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-interventions comparisons. However, it should be emphasised that randomised efficacy data present an idealised estimate of true effectiveness, and it is usually implausible that any differences between experimental and real-world settings would act to underestimate an intervention's 'true' effectiveness. Hence, preference will always be for high-quality randomised evidence when it comes to estimating the relative effects of different courses of action. Real world evidence may be considered if no or limited RCT evidence had been found. Cohort studies were not included also for this reason and for the difficulty of controlling for confounders.

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Question1: Limiting TAVI, if suitable, to adults with non-bicuspid SAS if surgery is unsuitable does not reflect current practice and the latest medical guidelines.</td><td></td></tr>
<tr><td>Edwards Lifesciences</td><td>Evidence Review H: Interventions</td><td>109</td><td>003 - 010</td><td>1.5.1 Included studies
Aortic stenosis (non-bicuspid)

“Nine health economic studies with relevant comparisons were included in this review: 2 comparing only transcatheter aortic valve implantation to medical management and 5 comparing transcatheter aortic valve implantation to surgical aortic valve implantation. Two studies compared both transcatheter aortic valve implantation to medical management and transcatheter aortic valve implantation to surgical aortic valve implantation.”

We regret that the review of the health economic evidence is non-exhaustive and included only 9 studies. We identified 3 additional peer-reviewed cost-effectiveness publications with relevant comparisons that should have been included in this review. The studies are listed in the table below:

<table><tr><th>Publication Reference</th><th>Indication</th><th>Device</th><th>Country</th><th>Perspective</th><th>Comparator</th></tr><tr><td>Zhou et al. 2019 [37]</td><td>Intermediate Risk</td><td>SAPIEN 3</td><td>Australia</td><td>Health care system</td><td>SAV</td></tr></table></td><td>Thank you for drawing our attention to these economic evaluations that were inadvertently omitted from the guideline review.

The guideline’s own economic model has now been thoroughly revised in response to stakeholder comments.

We note some similarities between the results of the revised guideline model and that of those the omitted published models and health technology assessments. In particular, the estimates of quality-adjusted life-years are very similar. The most significant difference is the cost of the TAVI valve, which the cost-effectiveness results are very sensitive to. The two Australian studies used a price equivalent to £12,700, which is considerably below the £17,500 that is the mean cost of a TAVI valve paid by the NHS. The</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response

Pinar et al.2021 [38]	High Risk, Intermediate Risk, Inoperable	SAPIEN 3	Spain	Spain NHS	SAVR, SAVR, MM	€ 5 471, € 8 119, € 9 948
Zhou et al.2020 [39]	Low Risk	SAPIEN 3	Australia	3rd party payer	SAVR	AUD 3 521

SAVR: Surgical Aortic Valve Replacement MM: Medical Management

The studies in the table above demonstrate that TAVI with SAPIEN and SAPIEN 3 is cost-effective and in certain cases, dominant against SAVR. Many of these are recent cost-effectiveness evidence with SAPIEN 3, the valve in current clinical practice. Hence, we expect them to be considered in the review for a comprehensive appraisal of the cost-effectiveness conclusions drawn in the guideline's economic analysis of TAVI.

We also regret that the health economic evidence review did not include available economic evaluation from Health Technology Assessments, which are listed in the table below:

HTA	Country	Indication	TAVI device	Comparator	ICER
HIQA (Irish HTA)	Ireland	Intermediate Risk	SAPIEN XT	SAVR	Dominant
HIQA (Irish HTA)	Ireland	Low Risk	SAPIEN 3	SAVR	Dominant
NIPH (Norwegian HTA)	Norway	Low Risk	SAPIEN 3	SAVR	Dominant

Valve price in the other studies is not transparent but it seems likely they also use a price lower than the mean NHS price, since the differential intervention costs are much lower than in the revised guideline model.

Had those models used the same TAVI valve price as the guideline model, it is likely they would have reached a similar conclusion regarding cost effectiveness.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<table><tr><td>**HAS** (French HTA)</td><td>France</td><td>Low Risk</td><td>SAPIEN 3</td><td>SAVR</td><td>Dominant</td></tr></table> SAVR: Surgical Aortic Valve Replacement The above relevant economic evaluations from published HTAs also demonstrate that TAVI with SAPIEN 3 or SAPIEN XT is dominant against SAVR. We believe that the inclusion of these studies in the review would have allowed to better contextualize the conclusions drawn in the guideline's economic analysis of TAVI.	
Edwards Lifesciences	Evidence Review H: Interventions	126	011-014	1.5.4.2 TAVI Model Treatment effect and data sources "Relative treatment effects were based on a meta-analysis of the papers included in the clinical review. Studies referring to different risk groups were pooled together. Baseline probabilities after SAVR were based on the papers included in the clinical review. Due to sample size issues, most of the probabilities were pooled together between intermediate- and high-risk group with the exception of the probability of dying which is different in the two risk groups." We are concerned with how the evidence for different risk groups is pooled together – mixing type of devices (balloon-expandable vs. self-expandable), generation of valves and access route that do not reflect current practice.	Thank you for your comment. Baseline risks now are informed by NICOR audit 2019-2020 with the exception of mortality which is informed by the latest NACSA surgery audit. Following further committee discussion, it was agreed to use in the base case scenario relative treatment effects estimated from trials evaluating only 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to account for recent technological improvements. These are predominantly on the transfemoral

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Given the technological advancements and procedural improvements in TAVI over the past decade, we believe it is important to assess study outcomes in the context of the devices used and the study period. In this regard, we believe that 3 dimensions should not be pooled but looked at separately: 1. **TAVI major improvements with latest generation of devices** There is a large body of evidence demonstrating the improvements of outcomes with the valve's generation. A recent meta-analysis published in NATURE Scientific Research (Winter et al.2020) addressed "**TAVR with contemporary next generation devices has led to an impressive improvement in TAVR safety** driven by refined case selection, improved procedural techniques and increased site experience." We are concerned that **most of the evidence used is not based on the latest technology currently in use in the UK**. An example is SAPIEN 3 balloon expandable valve, which was launched in 2014; only one RCT (PARTNER 3 trial) has been considered (low-risk patients using transfemoral approach) within this draft guidance. We believe a 2021 Guidance on HVD should reflect current practice and not be influenced negatively by first-generation technology and/or evidence that would not reflect current practice. 2. **Transfemoral Approach representing nowadays 95%+ of all TAVI interventions.** Transfemoral approach is the preferred approach and is also a critical criteria in the latest guidelines favouring TAVI vs. surgery. Early trials were mixing transfemoral with other types of approach	approach. The analysis was undertaken with the goal of assessing whether TAVI was cost-effective compared to surgery, therefore evidence on balloon expandable and self-expandable valves were pooled together. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(transapical, subclavian, transthoracic, etc.). In the Siontis et al. 2019[35] meta-analysis, we clearly see the difference between the 2 approaches as: • Transfemoral favouring TAVI: pooled HR = 0.83 with 95% CI [0.72 – 0.94] • Transthoracic favouring Surgery (not statistically significant thought): pooled HR = 1.17 with 95% CI [0.88 – 1.55] Another example is our PARTNER 3 trial for low-risk patients: only transfemoral access route was used as if not feasible it was an exclusion criteria. **3. Different type of TAVI (balloon vs. self-expandable)** We would also like to stress that there are **important differences** for certain outcomes **between balloon-expandable valves** (SAPIEN family) and **self-expandable valves** (CoreValve Evolut, Portico, Accurate NEO, etc.). The best example is the risk of permanent pacemaker implantation – which differ dramatically between the 2 type of TAVI device[ix,xxiv,xxv,xxvi,xxvii,xxviii,xxix,xxx] We are also concerned that for the calculation of the baseline probabilities and the relative treatment effects for the same set of events, there is inconsistency in the selection of studies across the TAVI and the SAVR arms. For example, to calculate the relative treatment effects for the events in the TAVI arm, six studies from the clinical review- two high risk (Adams et al.2014[44], Smith et al.2011[24]), two intermediate risk (Leon et al.2016[45], Reardon et al.2017[46]) and two low risk (Mack et al.2019[47] and Thyregod et al.2015[48]) were used. Whilst for the same set of events in the SAVR arm, only the two high risk and the two intermediate risk studies were used.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We strongly suggest considering current generation of devices in use, differentiating between balloon-expandable vs. self-expandable (as has been done in the Ontario HTA) and focusing on the preferred transfemoral approach, representing 95%+ of all TAVI cases.	
Edwards Lifesciences	Evidence Review H: Interventions	126	014 - 016	1.5.4.2 TAVI Model Treatment effect and data sources "Due to sample size issues, most of the probabilities were pooled together between intermediate- and high-risk group with the exception of the probability of dying which is different in the two risk groups." The choice to pool together the probabilities between intermediate and high-risk group for all events except mortality is not clearly justified. It is unclear why the sample size issue does not apply to the event 'Death' when the pooled probabilities were obtained from the same set of studies (Adams et al.2014[44], Smith et al.2011[24], Leon et al.2016[45] and Reardon et al.2017[46]) as evidenced from the table below from HVD TAVI Model.xlsm (Sheet D5 Stratification). **High risk** | **Interm** **Events (r)** | **At risk (n)** | **Events (r)** **Mortality** | **Mo**	Thank you for your comment. To reflect contemporary outcomes of TAVI, the model was revised to use the latest UK NICOR audit. This audit unfortunately does not provide results stratified by risks so TAVI baseline probabilities could not be stratified. Mortality is informed by the latest NACSA audit and was stratified as the audit reports mortality according to the risk. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.

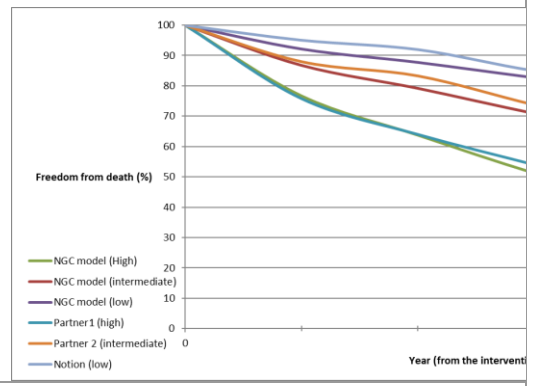
Adams et al.2014[44]	16	357		Leon et al.2016[45]	41	1021	
Smith et al.2011[24]	22	351		Reardon et al.2017[46]	11	867	
	Stroke				**Stroke**		
Adams et al.2014[44]	22	357		Leon et al.2016[45]	65	1021	
Smith et al.2011[24]	8	351		Reardon et al.2017[46]	46	867	
	Major bleeding				**Major bleeding**		
Adams et al.2014[44]	123	357		Leon et al.2016[45]	442	1021	
Smith et al.2011[24]	67	351		Reardon et al.2017[46]	73	784	
	Pacemaker implantation				**Pacemaker implantation**		
Adams et al.2014[44]	25	357		Leon et al.2016[45]	68	1021	
Smith et al.2011[24]	12	351		Reardon et al.2017[46]	53	796	
	Major vascular complications				**Major vascular complications**		

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Adams et al.2014[44] 6 357; Leon et al.2016[45] 51 1021; Smith et al.2011[24] 11 351; Reardon et al.2017[46] 9 796 We believe that instead of pooling the probabilities for all non-fatal events across risk groups it would have been more accurate to calculate the event specific probabilities for intermediate and high risk respectively (as was done for the event 'Mortality').	
Edwards Lifesciences	Evidence Review H: Interventions	126	008-009	1.5.4.2 TAVI Model Model Structure "Reintervention is assumed to be an additional surgery or TAVI based on the current activity level in England" We are concerned that the model structure assumes reintervention with SAVR after an initial TAVI procedure. This assumption clearly does not reflect common practice and very sparse research on this topic (e.g. Jawitz et al.2020 [40], Kothapalli et al.2020 [41], Pibarot et al.2020[16]) is non-conclusive. In fact, a Valve-in-Valve (ViV) TAVI or a re-do open heart surgical approach (re-do SAVR) is the norm (eg. Pibarot et al.2020[16]) and we already have some strong evidence showing the superiority of TAVI ViV vs. re-do SAVR (Deharo et al. 2020[42] and Tam et al. 2020[43]). Moving	Thank you for your comment. We have changed the reintervention rates using data from Pibarot 2020 although we are aware these percentages are based on a small sample size. Nevertheless, we do not expect this to change the model results considerably.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				forward, we also believe that TAVI ViV will be the preferred option over a re-do SAVR to treat a failed bioprosthesis (TAVI or biological SAVR).	
Edwards Lifesciences	Evidence Review H: Interventions	126	017 - 018	1.5.4.2 TAVI Model Treatment effect and data sources "Mortality was based on a study comparing mortality in the UK TAVI registry with the one of the general populations." Mortality for 'Stable with TAVI' health state was informed from the Martin et al.2017[49] study. This study is based on the UK TAVI registry (2007-2014), where one of the valves used was SAPIEN. The mortality outcomes would clearly not reflect what we could expect nowadays with SAPIEN 3 in current practice. Interestingly, the survival rate in the PARTNER 3 trial with SAPIEN 3 for low-risk patients outweigh the expected survival rate from the general population.	Thank you. Martin et al 2017 was chosen as it reports relative survival in the UK after TAVI. We decided to use the last data points available: 2011-2014. Although, as shown in the figure below, survival calculated through this approach matches survival of other low-risk cohorts (e.g. Notion trial), we are aware that the introduction of new generation valves occurred in the recent years may have pushed up survival curve, at least for the low-risk. Therefore, we added a new sensitivity analysis in the model where survival in the low-risk population is assumed to be equal to survival in the general population, which is in line with the short-term findings of PARTNER 3. Mortality in the other risk groups is calculated by applying the corresponding HRs to the new mortality rates of low risk people. Overall, this sensitivity analysis makes

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI slightly more cost effective than it was before but does not change the conclusions of the base case scenario analysis. 
Edwards Lifesciences	Evidence Review H: Interventions	130	034	1.7.1.1 The outcomes that matter most In our view, the primary outcomes (critical outcomes) and the secondary outcomes (important outcomes) identified in the review protocol (Appendix A of the review document) do not reflect the primary and the secondary outcomes in the RCT. Hence **a clinical outcome that is considered as secondary in the RCT should not be classified as primary outcome (critical outcome) for the purpose this review**. In fact the methodology for the statistical analysis would be built slightly differently for the primary and secondary outcome measurement in the RCT: Estimation of the	Thank you for your comment. In NICE reviews, critical and important outcomes refer to the weighting that they are given when making decisions about the evidence presented to the committee for a particular review. For example, the committee might interpret that an observed benefit for the critical outcome of mortality may

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				sample size, the trial power, non-inferiority and/or superiority testing boundaries are set based on the primary endpoints of the RCT (critical). This was the case for the PARTNER 3 trial for example, where the **primary endpoint was the composite of all-cause mortality, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1-year post-procedure**. While for key secondary endpoints, testing for superiority was performed in a prespecified hierarchical order (gatekeeping method) to control for multiple comparisons, for other secondary endpoints analysis were performed without correction for multiple comparisons. Considering all the above, and for the purpose of the Evidence review, **we would suggest the following changes (modification in bold text)** in the Primary (critical) and secondary (important) outcomes considered: Primary outcomes (critical outcomes) • All-cause mortality at ≥12 months • **All Stroke (all levels of severity) at 30 days** • **Re-hospitalisation at ≥12 months** • Cardiac mortality at ≥12 months • Intervention-related mortality at 30 days • ~~**Health-related quality of life at ≥12 months**~~ • Onset or exacerbation of heart failure at ≥12 months • ~~**Intervention-related stroke or TIA at 30 days**~~ • Intervention-related major bleeding at 30 days • Need for re-intervention at ≥12 months	outweigh an observed harm/worse outcome in an important outcome, such as length of stay or atrial fibrillation. Whether an outcome is considered to be critical or important was decided during protocol development, prior to studies being identified and included, meaning it is not possible to match these to the primary and secondary outcomes as reported in studies. Risk of bias assessment is performed at an outcome level so any differences in risk of bias across outcomes within a single study resulting from points highlighted in your comment should be captured if they impact on risk of bias, for example if attrition or missing data differ.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Secondary outcomes (important outcomes) • Length of stay (following initial intervention) • ~~**Re-hospitalisation at ≥12 months**~~ • Intervention-related pacemaker implantation at 30 days • Intervention-related atrial fibrillation at 30 days • Intervention-related major vascular complications at 30 days (defined as those requiring intervention for a vascular complication) • Prosthetic valve endocarditis at ≥12 months • **Health-related quality of life at ≥12 months** • **Myocardial infarction at 30 days and 1 year** • **Acute kidney injury at 30 days** • **Requirement for renal replacement therapy at 1 year** **Bioprosthetic valve dysfunction (i.e. paravalvular leak or endocarditis)**	
Edwards Lifesciences	Evidence Review H: Interventions	131	016	1.7.1.2. The quality of the evidence Aortic Stenosis (non-bicuspid) We regret that the evidence review was limiting the criteria to randomized controlled trials (RCT) only. Besides, the overall evidence selection criteria and the rational for the narrow evidence profile used (i.e. RCTs only) remains unclear to us. Especially that the Committee acknowledges (page 147, lines 9-12) that "*it is well established that interventions should be performed over conservative management and the reason there are no RCTs currently is because it would be unethical to include such a comparison within an RCT for the operable population*".	Thank you for your comment. It was agreed to be appropriate to limit to randomised data to inform this evidence review because this allows comparison between the available treatment options and limits confounding effects. The sentence you refer to on page 147, lines 9-12 contained an error which has since been corrected, as it should have read 'inoperable population' not 'operable population'.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This resulted in **excluding valuable evidence relative to transfemoral SAPIEN 3™ balloon expandable valve** used in current practice[i,ii,iii,iv]. Among the many important evidence excluded, several meta-analyses based on RCT and published in peer-reviewed journals[v,vi,vii,viii,ix]. Overall, the results from these meta-analyses showed that, compared with SAVR, **TAVI is associated with a statistically significant reduction in all-cause mortality, stroke and cardiovascular death**. The use of TAVI was also associated, compared to surgery, with **reduced risk of acute kidney injury, atrial fibrillation and major haemorrhage[ix] (p<0.01 for all).** In these studies the use **of SAPIEN 3™ balloon expandable valve** was also associated with a statistically significant **improvement in the quality of life of the patients** (measured by KCCQ-OS, SF-36 physical functioning scale and the SF- 36 mental health scale) at 1 month. This significant improvement in quality of life was **maintained at 1 year[i] and at 2 years (very recent publication by Leon et al 2021)[x]** follow-up. Question 1: We regret that the studies considered in the review are **not relevant to the transfemoral SAPIEN 3™ balloon expandable valve currently used in practice. Moreover, they were limited to the RCTs only.** Hence these recommendations, in our view, **do not represent the current clinical practice nor the current interventions used**. Considering the substantial clinical benefit **SAPIEN 3™ balloon expandable valve brings compared to the earlier SAPIEN devices, drawing such recommendations might put the patients' safety and health at stake.**	The revised version of the model calculates treatment effects from 2nd and 3rd generation valve only. These are predominantly assessing the transfemoral approach. In addition, the model includes a scenario analysis where reintervention treatment effect is calculated from Evolut and PARTNER 3 only, to account for the improvement of latest generation valves. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The first generations TAVI device Edwards **SAPIEN and SAPIEN XT™ are no longer used** in current practice since 2014 already. Unfortunately, the literature search and the RCTs included in the evidence review rely in the big majority on these initial generations of TAVI as follows: - The seven studies comparing transcatheter replacement versus standard surgery: SAPIEN (Nielsen et al 2012, Smith et al 2011) and SAPIEN XT (Leon et al 2016) - The study comparing transcatheter replacement versus pharmacological treatment: SAPIEN (Leon et al 2010) Hence **only one RCT** (Mack et al 2019) using **SAPIEN 3™, currently used in practice, was included in the evidence review.** The technical improvements are substantial between the early SAPIEN generations and **SAPIEN 3™ with a major impact on the clinical outcomes.** SAPIEN 3™ valve, launched in 2014, brings critical new technical features that have shown to significantly improve patients' outcomes[xi,xii] vs. the previous SAPIEN generations (SAPIEN and SAPIEN XT). The technical incremental improvements resulted also in **developing the transfemoral (TF) access route**. The latter is currently the standard practice and used in more than 95% of the cases, due to its **minimally invasive nature**, associated with shorter hospital stay and dispensing from general anesthesia. The meta-analysis by Tummala et al (2018)[xxxi] shows that compared to SAPIEN XT™, the innovations brought to SAPIEN 3™ improve critically the clinical outcomes (i.e. mortality, stroke, paravalvular leak…).	No previous meta-analyses were included directly in this clinical review. Available systematic reviews and meta-analyses, were assessed but provided insufficient information to be included and so were used for reference checking only. The meta-analysis by Tummala et al. (2018) was not included because it compared outcomes for SAPIEN 3 valve (S3V) and the SAPIEN XT (SXT) valve and did not therefore meet the review protocol criteria (see appendix A evidence review H). The other studies referred to did not meet the protocol criteria because they compared outcomes between different valve types.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Moreover, **additional recent studies** are available showing the differentiating benefit of **SAPIEN 3™ compared to previous SAPIEN™ generations**. In 2020, the 5-year follow-up data addressing the question of **durability and mid-term outcomes** of TAVI compared with SAVR were released (Juin 2020 TVT Connect conference by Kodali[xiii]). **The durability** question was also addressed by Pibarot et al (2020)[xiv] – using the latest VARC 3 definitions. The authors showed that the second generation of balloon-expandable valves, SAPIEN XT™, had lower midterm durability compared with surgery, whereas the third generation **SAPIEN 3™, had better durability compared with SAPIEN XT™** and was **similar to surgery**. The authors provided several explanations related to the valve technical features that result in lesser leaflet mechanical stress and thus better durability.	
Edwards Lifesciences	Evidence Review H: Interventions	132 133	039 - 044 001 - 049	1.7.1.3 Benefits and harms Aortic stenosis (non-bicuspid) Transcatheter replacement compared to surgery Question 1: We regret that the studies considered in the review are **not relevant to the Transfemoral SAPIEN 3™ balloon expandable valve currently used in practice. Moreover, were limited to the RCTs only.** Hence these recommendations seem to be, in our view, **do not represent the current clinical practice nor the current interventions used**. The use of the latest evidence, practice and technologies, together with the use of real-world evidence, are part of NICE 2021-2026 strategy released very recently.	Thank you for your comment. It was agreed to be appropriate to limit to randomised data to inform this evidence review because this allows comparison between the available treatment options and limits confounding effects, which is why the additional studies listed in relation to SAPIEN 3™ were not eligible for inclusion in the clinical review. The revised version of the model calculates treatment effects using

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Considering the substantial clinical benefit **SAPIEN 3™ balloon expandable valve brings compared to the earlier SAPIEN devices, drawing such recommendations might put the patients' safety and health at stake.** Many publications have shown the added clinical benefit of SAPIEN 3 balloon expandable valve compared to surgery in patients at increased surgical risks: The results of the comparative study between SAPIEN 3™ and surgical aortic valve replacement after propensity score matching conducted by Thourani *et al 2016* [xxxii]. (and for which three covariates were included, counting a total of 25 variables as described in previous sections) show that the use of the latest generation of SAPIEN 3™ bioprosthesis is associated, compared to surgery, with: • A significantly lower rate of all-cause mortality, stroke or aortic regurgitation ≥ moderate at 1 year (Adjusted difference: -7.6%; 95% CI: -11.5% to -3.7%; p=0,0002); • A significantly lower rate of major stroke and stroke of any type at 1 year (Adjusted difference major stroke: -6.5%; 95% CI: -9.1% to -3.8%; p <0,0001) (Adjusted difference for stroke all types: -3.1%; 95% CI: -5.5% to -0.6%; p <0.0135) • A significantly lower mortality rate at 1 year (Adjusted difference: -4.0%; 95% CI: -6.9% to -1.2%; p <0.0048). To better quantify the **SAPIEN 3 improvement** (vs. SAPIEN) **with transfemoral approach** for **high risk patients** (**HR**), we could compare	trials on 2nd and 3rd generation valves only. These are predominantly assessing the transfemoral approach. In addition, the model includes a scenario analysis where reintervention treatment effect is calculated from Evolut and PARTNER 3 only, to account for the improvement of latest generation valves. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Study designs to be included in each review were discussed with the

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>the RR (TAVI vs. SAVR) from the PARTNER 1A study from the Koldali study at 30 days and the Hermann study with SAPIEN 3 (same inclusion / exclusion criteria) at 1 year.

As we can see SAPIEN 3 significantly reduces the incidence of critical clinical outcomes at 30 days and 1 year.

<table>
<tr><th></th><th colspan="3">PARTNER 1A (Smith et al.2011, NEJM) *</th><th>Kodali et</th></tr>
<tr><th>30d Event - HR</th><th>SAPIEN</th><th>SAVR</th><th>RR</th><th>SAPIEN 3</th></tr>
<tr><td>Mortality</td><td>3.7%</td><td>8.2%</td><td>0.45</td><td>1.6%</td></tr>
<tr><td>Any Stroke</td><td>4.6%</td><td>1.4%</td><td>3.29</td><td>2.0%</td></tr>
<tr><td>Major Stroke</td><td>2.5%</td><td>1.4%</td><td>1.79</td><td>0.8%</td></tr>
<tr><td>Pacemaker</td><td>4.6%</td><td>4.2%</td><td>1.10</td><td>13.5%</td></tr>
<tr><td>Dialysis</td><td>3.4%</td><td>3.2%</td><td>1.06</td><td>0.8%</td></tr>
<tr><td>Major Bleeding</td><td>10.9%</td><td>23.1%</td><td>0.47</td><td>12.3%</td></tr>
<tr><td>Major Vasc.</td><td>14.2%</td><td>3.2%</td><td>4.44</td><td>5.5%</td></tr>
<tr><td>Re-hosp.</td><td>5.5%</td><td>4.8%</td><td>1.15</td><td>6.8%</td></tr>
</table>
** Compared to SAVR arm from Smith et al., 2011 NEJM</td><td>committee during the development of each review protocol and for this review there was considered to be enough RCT evidence, with no concerns about much of this evidence being from older generation devices raised. Therefore, non-randomised studies were not prioritised for this review</td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

	PARTNER 1A (Smith et al.2011, NEJM) *			Herman Circ
1y Event - HR	**SAPIEN**	**SAVR**	**RR**	**SAPIEN 3**
Mortality	21.3%	25.2%	**0.85**	10.7%
Any Stroke	6.1%	1.9%	**3.21**	
Major Stroke	3.5%	1.4%	**2.50**	
Pacemaker	5.5%	4.2%	**1.31**	
Dialysis	4.7%	5.5%	**0.85**	
Major Bleeding	15.9%	25.7%	**0.62**	
Major Vasc.	14.2%	3.2%	**4.44**	
Re-hosp.	17.5%	15.2%	**1.15**	

** Compared to SAVR arm from Smith et al., 2011 NEJM

To better quantify the **SAPIEN 3 improvement** (vs. SAPIEN) **with transfemoral approach** for i**ntermediate risk patients (IR)** at 30 days and 1 year, we could compare the RR (TAVI vs. SAVR) from the PARTNER 2A S3i study from the Thourani study with SAPIEN 3 (same inclusion / exclusion criteria) published in the Lancet.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				As we can see **SAPIEN 3 significantly reduces the incidence of critical clinical outcomes at 30 days and 1 year** (vs. SAVR and vs. NICE model at 30d)**.**	

	NICE Model			PARTNER 2A (Leon et al.2016, NEJM) *		
30d Event - IR	**SAPIEN**	**SAVR**	RR	**SAPIEN**	**SAVR**	**RR**
Mortality	2.42%	2.75%	**0.88**	3.0%	4.1%	**0.7**
Any Stroke	4.94%	5.43%	**0.91**	5.1%	6.5%	**0.7**
Major Stroke				2.3%	4.2%	**0.5**
Pacemaker	15.21%	6.26%	**2.43**	8.1%	7.1%	**1.1**
Dialysis	1.25%	2.85%	**0.44**	0.5%	3.0%	**0.1**
Major Bleeding	14.31%	28.05%	**0.51**	6.7%	41.4%	**0.1**
Major Vasc.	8.60%	3.05%	**2.82**	8.5%	3.9%	**2.1**
Re-hosp.				5.5%	6.5%	0.8

* From Appendix Table S6 ITT population
** From Appendix Table 3

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th colspan="3">PARTNER 2A (Leon et al.2016, NEJM) *</th><th colspan="2">Thourani et al.2016, Lancet **</th></tr>
<tr><th>1y Event - IR</th><th>SAPIEN</th><th>SAVR</th><th>RR</th><th>SAPIEN 3</th><th>RR **</th></tr>
<tr><td>Mortality</td><td>10.0%</td><td>12.3%</td><td>0.81</td><td>6.5%</td><td>0.53</td></tr>
<tr><td>Any Stroke</td><td>9.2%</td><td>10.0%</td><td>0.92</td><td>4.3%</td><td>0.43</td></tr>
<tr><td>Major Stroke</td><td>4.3%</td><td>6.0%</td><td>0.72</td><td>1.7%</td><td>0.28</td></tr>
<tr><td>Pacemaker</td><td>9.6%</td><td>9.5%</td><td>1.01</td><td>12.7%</td><td>1.34</td></tr>
<tr><td>Dialysis</td><td>2.2%</td><td>5.2%</td><td>0.42</td><td></td><td></td></tr>
<tr><td>Major Bleeding</td><td>11.1%</td><td>43.4%</td><td>0.26</td><td></td><td></td></tr>
<tr><td>Major Vasc.</td><td>8.8%</td><td>4.3%</td><td>2.05</td><td></td><td></td></tr>
<tr><td>Re-hosp.</td><td>13.1%</td><td>14.8%</td><td>0.89</td><td>10.5%</td><td>0.71</td></tr>
</table>
* From Appendix Table S6 ITT population
** From Appendix Table 3
</td><td></td></tr>
<tr><td>Edwards Lifesciences</td><td>Evidence Review H:</td><td>134</td><td>024 - 029</td><td>1.7.1.3 Benefits and harms
Aortic stenosis (non-bicuspid)
Transcatheter replacement compared to surgery</td><td>Thank you for your comment.

Evidence review H was an intervention review aimed at comparing outcomes between two</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	Interventions			"*The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated and this area was not prioritised for a research recommendation for the same reasons.*" As mentioned previously, the largest cohort analysis (**170,959 patients)** by Halim et al 2020**Error! Bookmark not defined.** compared TAVR for the treatment of AS in bicuspid versus tricuspid aortic valves. **The authors showed that there were no differences in one-year mortality, stroke, or major bleeding between the patients with bicuspid aortic valve and tricuspid aortic valve.** The use of **current-generation balloon-expandable valves was associated with a lower risk of significant paravalvular leak in patients with bicuspid AV than current-generation self-expanding valves.** The authors concluded that **TAVR is both safe and effective for the treatment of bicuspid aortic valve stenosis.** We call the Committee to update the recommendation and **consider both the bicuspid and non-bicuspid** aortic valve stenosis population per the 2020 AHA / ACC guidelines based on age, life expectancy and valve durability, as follows: • For symptomatic and asymptomatic patients with severe AS and any indication for surgery who are <65 years of age or have a life expectancy >20 years, surgery (by median sternotomy or minimally invasive 3 surgery) is recommended.	different interventions. Although this review was limited to RCTs, even if non-randomised studies had been included, the study described in your comment would not have been eligible for inclusion as it does not compare outcomes between two groups receiving different interventions. In addition, the committee noted that most people with bicuspid aortic valve disease would need aortic valve replacement at a much younger age, making them ineligible for TAVI. The recommendation made does not preclude it being performed in those with bicuspid aortic valve disease at all, but this population was not included in the recommendation due to a lack of RCT evidence in this specific population. The committee considered that dropping to lower levels of evidence would not inform a recommendation and due to the variation in current clinical practice they were unable to make consensus recommendations. The committee

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either surgery or transfemoral TAVI is recommended after shared decision making about the balance between expected patient longevity and valve durability. • For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to surgery. Regardless of age recommendations, the guidelines emphasize the importance of **shared decision making between the Heart Team and the patient** to determine the choice of treatment.	noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently and this area was not prioritised for a research recommendation for this reason.
Edwards Lifesciences	Evidence Review H: Interventions	134	030 - 031	1.7.1.3 Benefits and harms Aortic stenosis (non-bicuspid) Transcatheter replacement compared to surgery "The committee agreed that a cross referral to the NICE interventional procedure guidance (IPG586) on transcatheter aortic valve implantation for aortic stenosis was relevant." We are concerned that this draft guideline is not in line with the latest British clinical guidelines on TAVI for the indications and the different patient groups who could benefit from TAVI. Therefore, we strongly call NICE to consider the latest recommendations from the national and international scientific societies on the use of TAVI in patients with SAS. <u>Question 1:</u> we have major reservations with regards to the reference of this draft heart valve disease guideline, to outdated policy and guidance	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). See evidence review H for the clinical and health economic evidence that was considered. NICE guidelines do not consider other non-NICE guidelines when making their recommendations

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				from 2013 and 2017 respectively. In fact, **the commissioning policy on TAVI and the NICE guidance on TAVI, are no longer accurate enough and do not reflect the current practice in the UK in 2021**. Moreover, they are **inconsistent with the current British clinical guidelines on TAVI** (British Cardiovascular Intervention Society (BCIS) 2019) as well as the indications and patient groups who could benefit most from a minimally invasive intervention. The following are some additional major concerns we have: - 2013 NHS England's clinical commissioning policy on TAVI This policy dated from 2013, recommends TAVI for the Inoperable and for the high-risk patient (STS > 10%). Obviously, this document was published 8 years ago, hence it was **addressed before the release of evidence showing TAVI superiority compared to surgery for intermediate risk patients** (transfemoral subgroup in the PARTNER 2A trial) and for low-risk patients (PARTNER 3). We would like to draw your attention that the PARTNER 2A trial (Leon et al 2016) and PARTNER 3 trial (Mack et al 2019) were among the RCTs selected for this draft heart valve disease guideline, however they are not in the NHS England's commissioning policy on TAVI. - 2017 TAVI NICE interventional procedure guidance (IPG) The latest NICE IPG from 2017 already covered in its review the intermediate risk trials and assessed the TAVI benefits when transfemoral approach is feasible. However, **it does not include the low-risk patients** as the PARTNER 3 trial was published in 2019.	https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission The results of the HTAs mentioned differ from the conclusions of the model largely due to the lower price TAVI is purchased at in other countries. Sapien 3, for instance, is purchased in France at a price considerably lower than the one the NHS is charged (https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036577833). Likewise, the ONTARIO HTA assumes that the cost of the device is around £13,000, considerably lower than the average price of £17,500 under the NHSE High-Cost Tariff Excluded Devices Programme. At similar prices, the conclusions of NICE model would likely echo the conclusions of the HTAs.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				On a separate, the conclusion from the NICE guidance are inconsistent with recent **TAVI HTA reports' conclusions from other countries** (i.e. France (HAS 2020[36]), Norway (NIPH 2021[58]), Ireland (HIQA 2019[59]), Canada (Ontario Health 2020[60,61]). Overall, these HTA bodies, provided **positive recommendations for funding TAVI in patients with a severe symptomatic aortic valve stenosis who are at intermediate and low surgical risks.** The assessment of the clinical evidence, suggested that compared to surgery, **TAVI reduces all-cause mortality and disabling stroke, risk of major bleeding, and new-onset fibrillation**; and makes little or no difference for all-cause and cardiovascular mortality, Myocardial Infarction and stroke at long-term follow-up. TAVI is **associated with a shorter length of stay** in hospital following the procedure than SAVR and, as a less invasive procedure, delivers **additional health gains in terms of patients' health-related quality of life** in the short-term. Also, compared with SAVR, TAVI is considered a **highly cost-effective treatment option** for patients at low or intermediate surgical risk. The following are the key conclusions for each of the assessments: **Ireland - HIQA 2019 recommendations on TAVI**Error! Bookmark not defined. • ***"TAVI should be available for patients aged 70 years*** *and over with severe symptomatic aortic stenosis* ***at low and intermediate surgical risk*** *in the Irish public healthcare system.* • *The current clinical evidence suggests* ***TAVI is no less effective than SAVR in terms of cardiac and all-cause mortality****.* ***TAVI is associated with a shorter length of stay*** *in hospital following the*	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				procedure than SAVR and, as a less invasive procedure, ***delivers additional health gains in terms of patients' health-related quality of life in the short-term****.* • *Compared with SAVR,* ***TAVI is considered a highly cost-effective treatment option*** *for patients aged 70 years and over at low or intermediate surgical risk.* • *The estimated five-year budget impact of extending the TAVI care pathway to include approximately 100 patients at low and intermediate surgical risk* ***is likely to be budget neutral.*** *This estimate incorporates the cost of additional catheterisation laboratory capacity.* • *Greater use of TAVI as an alternative to SAVR will result in* ***shorter length of hospital stay and a reduced demand for ICU beds and theatre time, which may release resources to address demands elsewhere in the system.*** **Canada - Ontario Health Quality assessment 2020**Error! Bookmark not defined. *Both TAVI and SAVR improved symptoms and quality of life at 1 y after these procedures. TAVI is a less invasive procedure that results in* ***greater symptom improvement*** *and* ***quality of life*** *(GRADE: High), and in a* ***slight decrease in mortality*** *and* ***disabling stroke*** *(GRADE: Moderate) compared with SAVR at 30d after surgery. Mortality was similar between groups (1 y) (GRADE: Low); there was possibly a slightly lower risk of disabling stroke (1–2 y) (GRADE: Moderate and Low, respectively) with TAVI.* ***TAVI had a lower risk of life-threatening or disabling bleeding****, acute* ***kidney injury****, and* ***atrial fibrillation (GRADE: High) vs. SAVR****. A study that used a self-expanding TAVI valve showed TAVI had a higher risk of*	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				pacemaker implantation (GRADE: High), moderate-to-severe paravalvular regurgitation (GRADE: Moderate), and left bundle branch block (GRADE: High). The long-term clinical implications of these events are currently unknown. ***Shorter hospital stay for TAVI reduces financial and access burden**. Receiving TAVI can improve health outcomes for patients in the short term (30d after surgery). Receiving less-invasive TAVI can result in a shorter hospital stay and quicker return home."* **Norway- NIPH assessment of TAVI 2021** Error! Bookmark not defined. *"We conducted an overview of systematic reviews that included the two newest randomised trials on TAVI in low risk group published in May 2019. We included 15 systematic reviews (2 covering all risk groups, 11 the low risk group, and 2 the intermediate and low risk groups). Based on evidence from eight randomised trials, we conclude that TAVI compared with SAVR in patients with severe aortic stenosis across all surgical risk groups: **probably improves all-cause mortality** or **disabling stroke** up to two years may slightly **reduce major bleeding**, **new-onset fibrillation** and **acute kidney injury.** Health economic analysis was limited to the low surgical risk group, as the intermediate risk group was evaluated in a 2019 NIPH report. The cost-utility analysis in a lifetime perspective indicated that **TAVI was more effective (gain of 0.05 QALYs) and less costly (saving of NOK 35 000) than SAVR for patients with severe aortic stenosis at low surgical risk**.* **France – CNEDIMTS (HAS) Assessment of Edwards SAPIEN 3™ 2021**[xxxiii]	

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td><u>Added medical benefit (ASA/ASR):</u> ASA III (Moderate Improvement)
"The PARTNER 3 study is demonstrating a significant difference at 2 years follow-up between the SAPIEN 3 valve and SAVR for low risk sSAS patients on a composite endpoint [primary endpoint] defined as all-cause mortality, disabling stroke and re-hospitalisation. Each technique has its own complication: more bleeding and atrial fibrillation with SAVR and more thrombosis and mild PVL with SAPIEN 3 implanted by transfemoral approach. However, the SAPIEN 3 implantation via transfemoral approach is associated with a more rapid quality of life improvement, is a less invasive technique and is not associated with an increased risk of permanent pacemaker implantation."</td><td></td></tr>
<tr><td>Edwards Lifesciences</td><td>Evidence Review H: Interventions</td><td>144</td><td>026 - 040</td><td>1.7.2 Cost effectiveness and resources used.
Aortic Stenosis – Inoperable

We regret that the cost-effectiveness review for the inoperable AS patient group is not exhaustive. A relevant and partially applicable peer-reviewed publication assessing the cost-effectiveness of TAVI with SAPIEN 3 against medical management were not considered in the review.

<table>
<tr><th>Publication Reference</th><th>Indication</th><th>Device</th><th>Country</th><th>Perspective</th><th>Comparator</th><th>I</th></tr>
<tr><td>Pinar et al.2021 [38]</td><td>Inoperable</td><td>SAPIEN 3</td><td>Spain</td><td>Spain NHS</td><td>MM</td><td>€</td></tr>
</table>
</td><td>Thank you for drawing our attention to this economic evaluation that was inadvertently omitted from the guideline review. We noted that the results of this study are consistent with the studies that were included in the guideline review in showing TAVI to be cost effective compared to medical management for inoperable patients. The study was however selectively excluded from the review as other studies based on randomized controlled data were available.</td></tr>
</table>

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>MM: Medical Management</td><td></td></tr>
<tr><td>Edwards Lifesciences</td><td>Evidence Review H: Interventions</td><td>144-145</td><td>042 - 009</td><td>1.7.2 Cost effectiveness and resources used.
Aortic Stenosis - Operable

We regret that the cost-effectiveness review for the operable AS patient group is not exhaustive. Relevant and partially applicable peer-reviewed publications assessing the cost-effectiveness of TAVI against SAVR and listed in the table below, were not considered in the economic evidence review.

<table><tr><th>Publication Reference</th><th>Indication</th><th>Device</th><th>Country</th></tr><tr><td>Zhou et al. 2019 [37]</td><td>Intermediate Risk</td><td>SAPIEN 3</td><td>Australia</td></tr><tr><td>Pinar et al.2021 [38]</td><td>High Risk, Intermediate Risk</td><td>SAPIEN 3</td><td>Spain</td></tr></table>SAVR: Surgical Aortic Valve Replacement MM: Medical Management</td><td>Thank you for drawing our attention to these economic evaluations that were inadvertently omitted from the guideline review.

Pinar 2021 and Zhou 2019 were selectively excluded as other evidence based on randomized controlled data were available. Zhou 2020 was added to the review and can be found in evidence review H.

We note some similarities between the results of the revised guideline model and that of those the omitted published models and health technology assessments. In particular, the estimates of quality-adjusted life-years are very similar. The most significant difference is the cost of the TAVI valve, which the cost-effectiveness results are very sensitive to. The two Australian studies used a price equivalent to</td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					£12,700, which is considerably below the £17,500 that is the mean cost of a TAVI valve paid by the NHS. The valve price in the other studies is not transparent but it seems likely they also use a price lower than the mean NHS price, since the differential intervention costs are much lower than in the revised guideline model. Had those models used the same TAVI valve price as the guideline model, it is likely they would have reached a similar conclusion regarding cost effectiveness.
Edwards Lifesciences	Evidence Review H: Interventions	145	012 - 013	1.7.2 Cost effectiveness and resources used. Aortic Stenosis – Operable "Low operative risk patients were not studied in the model but are expected to have similar outcomes and costs of patients at intermediate operative risk." We are concerned that the outcomes and costs are presumed to be the same for low risk patients and intermediate risk patients. Published evidence on cost-effectiveness of SAPIEN 3 in low risk patients, which was not considered in the economic evidence review, refutes this assumption.	Thank you for your comment. The guideline's economic model has now been thoroughly revised in response to stakeholder comments. A separate analysis has now been conducted for a cohort of patients at low surgical risk. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<table><tr><th>Publication Reference</th><th>Indication</th><th>Device</th><th>Country</th><th>Perspective</th><th>Comparator</th><th>ICER</th></tr><tr><td>Zhou et al.2020 [39]</td><td>Low Risk</td><td>SAPIEN 3</td><td>Australia</td><td>3rd party payer</td><td>SAVR</td><td>AUD 52</td></tr></table> SAVR: Surgical Aortic Valve Replacement Similarly, published economic evaluation from Health Technology Assessments, which are listed in the table below, also clearly does not support the assumption. <table><tr><th>HTA</th><th>Country</th><th>Indication</th><th>TAVI device</th><th>Comparator</th><th>ICER</th></tr><tr><td>**HIQA** (Irish HTA)</td><td>Ireland</td><td>Intermediate Risk</td><td>SAPIEN XT</td><td>SAVR</td><td>Dominant</td></tr><tr><td>**HIQA** (Irish HTA)</td><td>Ireland</td><td>Low Risk</td><td>SAPIEN 3</td><td>SAVR</td><td>Dominant</td></tr><tr><td>**NIPH** (Norwegian HTA)</td><td>Norway</td><td>Low Risk</td><td>SAPIEN 3</td><td>SAVR</td><td>Dominant</td></tr><tr><td>**HAS** (French HTA)</td><td>France</td><td>Low Risk</td><td>SAPIEN 3</td><td>SAVR</td><td>Dominant</td></tr></table> SAVR: Surgical Aortic Valve Replacement	at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Thank you for drawing our attention to these economic evaluations that were inadvertently omitted from the guideline review. Zhou et al 2020 and NIPH (Norwegian HTA) have been added to the review (see evidence review H). The French HTA was excluded as we could not find an English version. HIQA HTA was excluded as non-applicable to the UK NHS as the cost of surgery appears to be significantly higher than the one reported in the UK (around £10,000 higher). More information can be found in Evidence Review H document.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Evidence Review H: Interventions	145	017 - 018	1.7.2 Cost effectiveness and resources used. Aortic Stenosis – Operable "the reintervention rate, which was substantially higher in the TAVI arm in the guideline model based on the results of the guideline's systematic review of trial evidence". Reintervention probability for the TAVI arm is informed by Ler et al.2020[50].There are two issues with the use of this study. Firstly, it is unclear why this study is used for the economic analysis while it was excluded in the clinical review for inadequate/unclear methods (Evidence Review H; Appendix 1.1, Table 62, page 544). Secondly, the PARTNER and PARTNER 2 trials were based on older generations of SAPIEN valves and hence we are concerned that there might be a bias in the calculated number of patients requiring reintervention in the TAVI arm. A recently published study, Pibarot et al.2020[16] demonstrates that the durability of SAPIEN 3 (valve in current practice) is better than with SAPIEN XT and similar to SAVR. Indeed, in this publication published in JACC (Impact factor = 20.6) the authors concluded "Compared with SAVR, the second-generation SAPIEN XT balloon-expandable valve has a higher 5-year rate of SVD, **whereas the third-generation SAPIEN 3 has a rate of SVD that was not different from SAVR**". The authors provided several explanations related to the	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review not using the GRADE system, though it was included as an evidence for the model as the absence of GRADE system was not considered a severe limitation. After further discussion, the committee agreed to exclude this evidence as it was clearly focused on old generation valves not reflecting contemporary practice, as your comment highlighted. Relative treatment effects for reintervention now come from the trials included in the literature review as these were extensively discussed and reviewed by the committee. In the base case analysis, we are only using the treatment effect captured in trials

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				valve technical features that result in lesser leaflet mechanical stress and thus better durability. Additionally, a recent study from Blackman, et al 2019[17] sought to evaluate the incidence of hemodynamic structural valve deterioration up **to 10 years following TAVR from the UK TAVI Registry**. The study found excellent overall long-term durability with TAVR valves. A recent multicenter study from France also confirmed promising long-term durability of TAVR valves. The study reported the **7-year** cumulative incidence of bioprosthetic valve failure (BVF) was 1.9%, and moderate and severe structural valve deterioration (SVD) was 7.0% and 4.2%, respectively. These outcomes were based on the newly published European criteria for BVF and SVD[18]. An observational study from Canada followed patients for 10 years after TAVI with early-generation THVs and concluded that there was **a low rate of structural valve deterioration and valve failure at 10-year follow-up** (6.5%) and a low rate of SVD/BVF (6.5%)[19,20]. Hence, by implication it can be expected that the risk of reintervention in the TAVI arm is overestimated in the study and clearly does not reflect current practice.	evaluating 2nd and 3rd generation valves: • PARTNER 2 • PARTNER 3 • EVOLUT In addition, there is a sensitivity analysis where this figure is instead calculated from Evolut and Partner 3 only, with a relative risk close to 1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Evidence Review H: Interventions	146	044 - 047	**Section 1.7.3: Other factors the committee took into account** **We regret that very limited evidence related to the impact of TAVI intervention on patients' quality of life and patients' preferences were considered in the evidence review.** We acknowledge that the draft guidelines repeatedly highlight the importance of a shared decision making, leveraging the decision for intervention on "*the benefit to quality of life (both in the short and long term)*" as well as on patients' preferences and experience. While we appreciate the above, we are very surprised that the **quality of life measures and outcomes were not considered further by the Committee** as part of the critical outcomes that matter most for the patients nor in the review of the benefits of TAVI. Although included in as part of the critical outcomes, in the assessment of the available evidence, the quality of life and more broadly the patient preferences were given very limited consideration. Moreover, this very partial consideration was amplified by the clinical studies selection method which excluded valuable evidence, as described above.	Thank you for your comment. All outcomes included in the review were considered when discussing the evidence as a committee and making decisions. The committee discussion section has been amended to make this clearer.
Edwards Lifesciences	General	General	General	Edwards Lifesciences is a pioneer innovator from mechanical to biological surgical valves and minimal invasive surgical valves, transcatheter aortic valve replacement and transcatheter mitral and tricuspid repair technologies. We are the major supplier to the NHS. The comments below come from the three heart valve disease divisions within Edwards: • Surgical Structural Heart Business Unit – Surgical and MIS valves • Transcatheter Heart Valve Business Unit – TAVI valves	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Transcatheter Mitral and Tricuspid Therapies – Mitral and Tricuspid repair	
Edwards Lifesciences	Guideline	006	005 - 019	**Referral and specialist assessment for pregnant women and women considering pregnancy** The choice of replacement valve for women of childbearing potential, recommendations were not considered regarding the type of valve they receive if surgery is performed, whereby further important differences are reported between mechanical and prosthetic valves. While we appreciate that a recommendation for referral and specialist assessment has been made within the draft guidance, we feel it important that a distinction between mechanical and prosthetic valves be made as it relates to pregnant women and women considering pregnancy, acknowledging the limited evidence available. We regret that the evidence review was limiting the criteria to RCTs only. We feel it important to highlight studies which would otherwise be excluded from selection, and which are important to this patient population as these studies do report higher rates of adverse pregnancy outcomes such as miscarriage and caesarean delivery with mechanical valves than with bioprosthetic valves. Some studies report higher rates of adverse maternal events such as post-partum haemorrhage and thromboembolic events with mechanical valves than with bioprosthetic valves. The necessity of anticoagulation for patients who receive mechanical valves is an important consideration for women who are contemplating becoming pregnant, as anticoagulation has been shown to increase the risk of complications during pregnancy. [8] [9] [10]	Thank you for your comment. Women who are pregnant were included in the evidence review on interventions (evidence review H). Type of valve was a subgroup if heterogeneity was identified. Unfortunately, no evidence was identified and due to variation in clinical practice the guideline committee were therefore unable to make any recommendations on this topic. The guideline committee considered that RCT evidence represented the best quality of evidence to inform recommendations in this area.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[8] Hirji SA, Kolkailah AA, Ramirez-Del VF, Lee J, McGurk S et al., "Mechanical Versus Bioprosthetic Aortic Valve Replacement in Patients Aged 50 Years and Younger.," Annals of Thoracic Surgery, Vols. 106 (4): 1113-1120., 2018. [9] McClure RS, McGurk S, Cevasco M, Maloney A, Gosev I et al. , "Late outcomes comparison of nonelderly patients with stented bioprosthetic and mechanical valves in the aortic position: a propensity-matched analysis.," Journal of Thoracic and Cardiovascular Surgery , Vols. 148 (5): 1931-1939, 2014. [10] Alex S, Hiebert B, Arora R, Menkis A, Shah P, "Survival and Long-Term Outcomes of Aortic Valve Replacement in Patients Aged 55 to 65 Years.," Thoracic and Cardiovascular Surgeon, Vols. 66 (4): 313-321, 2018.	

Edwards Lifesciences	Guideline	008	006	Section 1.3 – Indication for Intervention
				Recommendation for Aortic Stenosis (AS)
				
				The "normal" symptomatic severe aortic stenosis (sSAS) definition and recommendation is missing. The focus is on asymptomatic severe aortic stenosis (SAS) and on sSAS low-flow low gradient with LVEF < 50%. The recommendation for intervention is based on evidence that covers sSAS from a more "generic" approach. We suggest including a precise definition as mentioned in the following guidelines:
				• 2017 ESC Guidelines
				  ○ Figure 2 – page 2752
				  ○ Table 6 – page 2753
				• 2020 AHA / ACC Guidelines
				  ○ Aortic Vmax ≥4 m/s or mean ΔP ≥40 mm Hg
					Thank you for your comment. The recommendations are based on the indications as reported in the studies. These studies used the 'generic' definitions but the committee are confident they are meaningful to clinicians.
					
					We have expanded on our definition of suitability for TAVI in the section 'terms used in this guideline'
					The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				○ AVA typically ≤1.0 cm2 (or AVAi ≤0.6 cm2/m2) but may be larger with mixed AS/AR Question 1: The **lack of clear and pragmatic definition of the specific indication for TAVI** will be a challenge for the healthcare professionals and for the patients. Hence the lack of understanding will hinder a sound and shared decision making together with the patients. We regret that the draft guideline does not appropriately refer to the critical role of the multi-disciplinary hear team (MDT) in the shared decision making. This is highly emphasised in the national and international clinical guidelines as well as the NICE 2017 TAVI IPG. Each patient profile is different and has unique set of needs that **can be only evaluated by the expertise of the MDT**, and yet it is not catered for, specifically in the proposed draft guideline. Furthermore, not all TAVI valve systems have the necessary regulatory approvals for all the indications. Question 3: having a better definition of patients with sSAS and eligible for TAVI, per the latest updated clinical guidelines (national and international), can help subside the uncertainty around the appropriate patient profile who could benefit most from TAVI valve.	importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. We revised the economic model based on stakeholder comments. We have changed the recommendations and TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). Risk is defined according to the EuroSCORE II.
Edwards Lifesciences	Guideline	011	016 - 019	Section 1.5.2 This paragraph is too restrictive and should include the transcatheter alternative. If TAVI is the best option for the patient and it's not available locally, then the person should be referred to another centre. We propose the following wording as a replacement:	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"When the **procedure** is agreed, base the decision on the type of **procedure** (median sternotomy, **minimally invasive surgery or TAVI**) on patient characteristics and patient preferences. If minimally invasive surgery **or TAVI** is the agreed option and is not available locally, refer the person to another centre." Question 3: TAVI being the best alternative to surgery, the proposed options should not be limited to one intervention only, but all possible options should be proposed and discussed with the patients together with their risks and benefits. The more patients are aware about the treatment options they have and the risks/benefit, the more relevant is the shared decision with the healthcare professionals. On a separate note, we regret that the draft guideline does not appropriately refer to the critical role of the multi-disciplinary heart team (MDT) in the shared decision making per the national and international clinical guidelines. Each patient profile is different and has unique set of needs that **can be only evaluated by the expertise of the MDT.**	effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). We now therefore refer to transcatheter in the bullet point in recommendation 1.5.1 on type of access. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Edwards Lifesciences	Guideline	011	010 - 011	Section 1.5 – Interventions Section 1.5.1 - Decision about interventions We believe in the discussion under the "type of access for surgery" it is currently too restrictive and limited to surgery only as it does not include the access route for TAVI. We propose to include these approaches as well and phrase it as: "the type of access for surgery (median sternotomy or minimal invasive surgery) **or TAVI (transfemoral, transapical, subclavian, trans-thoracic, etc.)**.	Thank you for your comment. The review protocol (see Appendix A in evidence review H) did not include a comparison of the different types of access for TAVI. The committee did not highlight this as a priority for inclusion because the majority of access in the UK is transfemoral.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Question 3: TAVI being the best alternative to surgery, the proposed options should not be limited to one intervention only, but all possible options should be proposed and discussed with the patients. Moreover, considering that multiple access routes exist for TAVI, the different options should be proposed together with their risks and benefits. The more patients are aware about the treatment options they have and the risks/benefit, the more relevant is the shared decision with the healthcare professionals. On a separate note, we regret that the draft guideline does not appropriately refer to the critical role of the multi-disciplinary heart team (MDT) in the shared decision making per the national and international clinical guidelines. Each patient profile is different and has unique set of needs that **can be only evaluated by the expertise of the MDT.**	We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). We now therefore refer to transcatheter in the bullet point in recommendation 1.5.1 on type of access. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Edwards Lifesciences	Guideline	011	009	Section 1.5 – Interventions Section 1.5.1 - Decision about interventions	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We believe in the discussion under the "risks associated with the procedure" **the various procedure options (TAVI, surgery or Minimally invasive Surgery (MIS) should be mentioned**. TAVI is the standard of care for Inoperable, High Risk patients and is becoming for some Intermediate Risk (IR) and Low Risk (LR) patients (2019 BCIS acknowledging that 2017 ESC guidelines already outdated, 2020 AHA / ACC guideline) if transfemoral approach is feasible. Risk scores are not the critical discriminant anymore, but decision-making should be individualised based on patient-specific factors (longevity quality of life, comorbid cardiac and noncardiac conditions, frailty, dementia, and other factors). The age of the patient is replacing surgical risk as the basis for recommendations (2020 AHA / ACC guideline, various HTAs – HAS, NIPH, HIQA, Ontario Health). Question 3: providing visibility to the users and the patients about all available treatment options together with their risks and benefits. We believe this can help explore all options before the decision and consider the patients preferences accordingly.	TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). We now therefore refer to transcatheter in the bullet point in recommendation 1.5.1 on type of access. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Guideline	011	012	Section 1.5 – Interventions Section 1.5.1 - Decision about interventions We believe in the discussion under the "possible need for other cardiac procedures in the future" we should list the most suitable options and would propose to include in parenthesis "(re-do surgery or TAVI Valve-In-Valve)"	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					surgical risk (1.5.3). We now therefore refer to transcatheter in the bullet point in recommendation 1.5.1 on type of access. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Guideline	011 - 014	General	**Section 1.5 Intervention – Mechanical and Bioprosthetic Valves** A distinction between mechanical and bioprosthetic valves should be considered in the guideline to inform the Multidisciplinary Heart Team for patients being considered for surgery. Current and updated treatment guidelines (2020 American College of Cardiology/American Heart Association (ACC/AHA) and 2017 European Society of Cardiology/European Association of Cardio-thoracic Surgery (ESC/EACTS) distinguish between mechanical and bioprosthetic valves, with the 2020 ACC/AHA Guidelines having recently lowered the age threshold and therefore do recommend bioprosthetic Aortic Valve Replacement (AVR) from 70 years to 65 years (Class 2A). ESC/EACTS guidelines will be updated on August 2021. We encourage this guidance to refer to UK practice and to incorporate recent recommendations published in a National Institute for Cardiovascular Outcomes Research (NICOR) 2020 SUMMARY Report, in the National Adult Cardiac Surgery Audit (NACSA). Recommendations were made in patients <60 years old undergoing surgical AVR where the	Thank you for your comment. Valve type was a subgroup which would be explored if heterogeneity was found. However, as no heterogeneity was found this was not explored.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				benefit of avoiding anticoagulation has to be carefully weighed against the high likelihood of needing further intervention in the future (either by redo surgery or TAVI) and the cost to the NHS and risk to the patient that is involved in the longer term. Bioprosthetic aortic valve implantation is not recommended in patients <60 years old who are likely to need anticoagulation for a reason other than for their prosthetic valve. NICOR (2020) The selection of a prosthetic valve is a multifactorial decision that should include the patient, the physician/surgeon, and the heart team [1] [2] Factors/characteristics associated with both the prosthesis and the patient must be considered. Prosthesis-related factors include hemodynamics, thrombogenicity, valve durability, and risk of reoperation. Bioprosthetic valves have lower thrombogenicity than mechanical valves, but there is a higher risk of reoperation associated with structural valve degeneration/deterioration (SVD) [1] [2]. Although this remains an important consideration, technical advancements in valve design have improved the durability of modern bioprosthetic valves [7]. Patient-related factors include age, life expectancy, lifestyle, medication adherence, comorbidities, and contraindications for anticoagulation. Younger patients are more likely to require reoperation with bioprosthetic valves, but the high thrombogenicity of mechanical valves necessitates lifelong anticoagulation (usually with warfarin) leading to an increased risk of bleeding [1] [2]. Because of the bleeding risk, frequent international normalized ratio (INR) testing is required for patients with mechanical valves [1] [2]. In addition, patients on warfarin are required to make	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				substantial lifestyle changes, including dietary monitoring and adjustments and activity limitations [3]. Notably, anticoagulation increases the risk of complications during pregnancy, which is an important consideration for female patients who are considering having children [1] [2] [4]. Finally, some patients may be disturbed by the audible clicking sound that occurs when a mechanical valve closes, which can further impact QoL [5] [6]. [1] Attia T, Yang Y, Svensson LG, Toth AJ, Rajeswaran J, Blackstone EH, Johnston DR, members of the Cleveland Clinic Aortic Valve Center,, "Similar Long-term Survival after Isolated Bioprosthetic versus Mechanical Aortic Valve Replacement: A Propensity-Matched Analysis," The Journal of Thoracic and Cardiovascular Surgery, p. https://doi.org/10.1016/j.jtcvs.2020.11.181, 2021. [2] Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al.; , "ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease.," Eur J Cardiothorac Surg. , no. 52(4):616–64. doi:. http://dx.doi.org/10.1093/ejcts/ez, 2017. [3] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd et al. , "2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.," Circulation , Vols. 135 (25): e1159-e1195, 2017. [4] Otto CM, Nishimura RA, Bonow RO, et al., "2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Committee on Clinical Practice Guidelines.," J Am Coll Cardiol. , vol. 2021; https://doi.org/10.1016/j.jacc.2020.11.018, 2020 [5 Stassano P, Di TL, Monaco M, Iorio F, Pepino P et al. , "Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years.," Journal of the American College of Cardiology, Vols. 54 (20): 1862-1868., 2009. [6] Schnittman SR, Adams DH, Itagaki S, Toyoda N, Egorova NN et al. , "Bioprosthetic aortic valve replacement: Revisiting prosthesis choice in patients younger than 50 years old.," Journal of Thoracic and Cardiovascular Surgery, Vols. 155 (2): 539-547., 2018. [7] Kheradvar A, Groves EM, Goergen CJ, Alavi SH, Tranquillo R et al, "Emerging trends in heart valve engineering: Part II. Novel and standard technologies for aortic valve replacement.," Ann Biomed Eng, Vols. 43 (4): 844-857., 2015.	
Edwards Lifesciences	Guideline	012	008 - 012	Section 1.5.3 We are concerned by the lack of clarity and positioning in the current draft guideline, and the reference to the 2013 NHS Commissioning policy on TAVI for AS, and to the 2017 NICE IPG on TAVI for AS. The three recommendations are inconsistent with the **latest medical guidelines** (2019 BCIS, 2017 Joint Statement BCS-SCTS-BCIS, 2017 ESC, 2020 AHA / ACC), **and the current practice in the UK.** To avoid any misinterpretation, we suggest to clearly define the indications – which currently should not be based on risk scores but more on patient's anatomy and age – after shared decision making based on the patients'	Thank you for your comment. In response to stakeholder comments and revisions to the economic model the committee agreed to revisit TAVI and have now recommend TAVI for people at high risk of surgery. This is in line with the 2013 NHS Commissioning policy on TAVI for AS, and the 2017 NICE IPG on TAVI for AS The recommendations in this guideline are based on the current

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				age, and the balance between life-expectancy and the valve durability per the updated 2020 AHA / ACC guidelines: For AS in adults: • For symptomatic and asymptomatic patients with SAS and any indication for surgery who are <65 years of age or have a life expectancy >20 years, surgery (by median sternotomy or minimally invasive 3 surgery) is recommended. • For symptomatic patients with SAS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either surgery or transfemoral TAVI is recommended after shared decision making about the balance between expected patient longevity and valve durability. • For symptomatic patients with SAS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to surgery. Regardless of age recommendations, the guidelines emphasize the importance of **shared decision making between the Heart Team and the patient** to determine the choice of treatment. For Aortic Regurgitation or Mixed aortic valve disease in adults Offer surgery, if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention.	clinical and health economic evidence considered in accordance with NICE processes https://www.nice.org.uk/process/pmg20/chapter/introduction and the recommendations may therefore differ from other guidelines. Recommendations under 'decisions about interventions' includes consideration of life expectancy and age under 'the benefits to quality of life (both in the short and long term) and also valve durability when making decisions about interventions. This recommendation also emphasises the importance of shared decision making and references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. The clinical and cost effectiveness of MDTs was not included in the scope

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). See evidence review H. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Guideline	012	008 - 012	Section 1.5.3 and the reference to the 2013 NHS England's clinical commissioning policy on transcatheter aortic valve implantation for AS and the recommendations on using TAVI in the 2017 NICE interventional procedures guidance on transcatheter aortic valve implantation for AS.	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We are concerned that this draft guideline is not in line with the latest British clinical guidelines on TAVI for the indications and the different patient groups who could benefit from TAVI. Therefore, we strongly call NICE to consider the latest recommendations from the national and international scientific societies on the use of TAVI in patients with SAS. Question 1: we have major reservations with regards to the reference of this draft heart valve disease guideline, to outdated policy and guidance from 2013 and 2017 respectively. In fact, **the commissioning policy on TAVI and the NICE guidance on TAVI, are no longer accurate enough and do not reflect the current practice in the UK in 2021**. Moreover, they are **inconsistent with the current British clinical guidelines on TAVI** (British Cardiovascular Intervention Society (BCIS) 2019) as well as the indications and patient groups who could benefit most from a minimally invasive intervention. The following are the current sources: • PARTNER 3 trial was published in 2019 (Mack 2019 and Leon 2021) • TAVI HTA reports: France (HAS 2020), Norway (NIPH 2021), Ireland (HIQA 2019), Canada (Ontario Health 2019 and 2020).	criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Guideline	012	003 - 005	Aortic Valve Disease – 1.5.3 "Offer surgery if suitable (by median sternotomy or minimally invasive surgery) as first-line intervention for adults with severe aortic stenosis…"	Thank you for your comment. We have revised the economic model based on stakeholder comments and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This recommendation does not reflect current clinical practice and the latest medical guidelines (2019 BCIS, 2017 Joint Statement BCS-SCTS-BCIS, 2017 ESC, 2020 AHA / ACC), **latest HTAs** (HAS, NIPH, HIQA, Ontario Health). Question 1: we are deeply concerned that transcatheter procedures will be excluded with this draft guideline and not recommended to patients that could benefit highly from the non-invasive procedure. A clear patient stratification should be proposed to the healthcare professionals and to the patients to make an informed decision, in line with the most updated clinical recommendations. The use of the latest evidence, practice and technologies is also in line with NICE 2021-2026 strategy released very recently. We suggest the following wording specifically for AS, which is aligned with the updated 2020 AHA / ACC guidelines and is based on age, life expectancy and valve durability: For AS in adults: • For symptomatic and asymptomatic patients with SSAS and any indication for surgery who are <65 years of age or have a life expectancy >20 years, surgery (by median sternotomy or minimally invasive 3 surgery) is recommended. • For symptomatic patients with SAS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either surgery or transfemoral TAVI is recommended after shared decision	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation. Recommendations under 'decisions about interventions' emphasise the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				making about the balance between expected patient longevity and valve durability. • For symptomatic patients with SAS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to surgery. Regardless of age recommendations, the guidelines emphasize the importance of **shared decision making between the Heart Team and the patient** to determine the choice of treatment. For Aortic Regurgitation or Mixed aortic valve disease in adults Offer surgery, if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention.	importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Edwards Lifesciences	Guideline	012	006-007	Limiting TAVI, if suitable, to adults with non-bicuspid SAS if surgery is unsuitable **does not reflect current practice and the latest medical guidelines** (per comment #21 above). The use of the latest evidence, practice and technologies is part of the NICE 2021-2026 strategy released very recently. We suggest the same wording than above for non-bicuspid AS adult patients (aligned with 2020 AHA / ACC guidelines based on age, life expectancy and valve durability):	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• For symptomatic and asymptomatic patients with SAS and any indication for surgery who are <65 years of age or have a life expectancy >20 years, surgery (by median sternotomy or minimally invasive 3 surgery) is recommended. • For symptomatic patients with SAS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either surgery or transfemoral TAVI is recommended after shared decision making about the balance between expected patient longevity and valve durability. • For symptomatic patients with SAS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to surgery. Regardless of age recommendations, the guidelines emphasise the importance of **shared decision making between the Heart Team and the patient** to determine the choice of treatment. For patients with bicuspid valve, there is strong evidence from real world practice demonstrating that TAVI performs as good as for tricuspid valve (Halim 2020[xxxiv]) – ensuring *"TAVI is a viable treatment option for patients with bicuspid AV disease"*.	currently, meaning evidence should not be extrapolated.
Edwards Lifesciences	Guideline	013	011	We would like to remind that additional RCT are currently enrolling patients to further evaluate the use of TEER for both primary and secondary MR: • Primary MR: ○ RESHAPE-HF2 trial (NCT02444338) will randomize 650 (according to the revised plan) patients with symptomatic heart	Thank you for your comment. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				failure (HF) (NYHA class II, III or ambulatory IV), Left Ventricular Ejection Fraction 15–45%, a history of at least one HF hospitalization within the previous year or increased natriuretic peptide levels, and moderate-severe or severe secondary mitral regurgitation (EROA ≥ 30 mm2) to MitraClip implantation plus GDMT or GDMT alone. The primary endpoint is cardiovascular death or recurrent HF hospitalization, and results are expected in 2022. ○ CLASP IID trial (NCT03706833) will randomize 300 patients (2:1 ratio) with primary MR and determined to be at prohibitive risk for mitral valve surgery by a Heart Team to PASCAL implantation or MitraClip implantation. The primary safety endpoint is a composite of Major Adverse Event at 30 days while the primary efficacy endpoint is the proportion of patients with MR severity reduction as measured by echocardiography. Primary results are expected in 2023. • Secondary MR: CLASP IIF trial (NCT03706833) will randomize 450 patients (1:1 ratio) with secondary MR and determined to be at prohibitive risk for mitral valve surgery by a Heart Team to PASCAL implantation plus GDMT or MitraClip implantation plus GDMT. The primary safety endpoint is a composite of Major Adverse Event at 30 days while the primary efficacy endpoint is the time to first heart failure hospitalization or death. Primary results are expected in 2023.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Guideline	014	003	Secondary mitral regurgitation (MR) - Section 1.5.13 Indication for TEER for secondary MR is **not reflecting latest recommendations from medical societies** as well as latest clinical data available. • We would like to emphasize that **TEER has been recommended (IIa level) by the ACC/AHA** in the latest 2020 guidelines [1]. This recommendation has not been considered in this current guideline. • In addition to the recommendation from the ACC/AHA, the latest joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology **emphasizes that TEER is an evidence-based treatment option in patients with severe secondary MR who remain symptomatic despite Guideline-Directed Medical Therapy (GDMT) and who have been carefully selected by a multidisciplinary Heart Team** [2]. This European joint statement has not been considered in the current guideline. [1] Otto CM et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143:e72-e227. [2] Andrew J.S. Coats et al. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from	Thank you for your comment. The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management. The current recommendation does not preclude mitral edge-to-edge repair being undertaken if medical management fails to control symptoms. We have added a recommendation to make this clearer (1.5.14).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC European Heart Journal (2021) 00, 1–16 doi:10.1093/eurheartj/ehab086.	
Edwards Lifesciences	Guideline	014	003	We underline a lack of alignment between the NICE Interventional Procedure Guidance [IPG649] recommendation and the current guideline. Indeed, the NICE IPG states that "Current evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is adequate to support the use of this procedure, in patients for whom open surgery is contraindicated following risk assessment" and there is no distinction between primary MR or secondary MR within this IPG.	Thank you for your comment. IPG649 did not consider the cost effectiveness of the procedure. This guideline undertook original health economic modelling in this area. This was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management. The current recommendation does not preclude mitral edge-to-edge repair being undertaken if medical

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					management fails to control symptoms. We have added a recommendation to make this clearer (1.5.14).
Edwards Lifesciences	Guideline	018	011	We would like to remind that additional RCT are currently enrolling patients to evaluate the use of TEER for TR: • CLASP II TR trial (NCT04097145) will randomize 450 patients (2:1 ratio) with symptomatic severe TR to PASCAL implantation plus GDMT or GDMT alone. The primary endpoint is a composite of adverse events including mortality, heart failure hospitalization, need for surgery on the tricuspid valve, and improvement of quality of life at 24 months. TRILUMINATE trial (NCT03904147) will randomize 450 patients (1:1 ratio) with symptomatic severe TR to TriClip implantation plus GDMT or GDMT alone. The primary endpoint is a Hierarchical composite of number of participants with all-cause mortality or number of participants with tricuspid valve surgery, rate of heart failure hospitalizations, and assessment of quality of life improvement using the KCCQ at 12 months.	Thank you for your comment. The committee has made a research recommendation on the optimal management strategy for tricuspid regurgitation. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Edwards Lifesciences	Guideline	036	003 - 005	Rational why the committee made the recommendations. AS when surgery is suitable. We believe the following statement does not reflect the reality in terms of TAVI's benefits versus surgery: "Evidence from 7 randomised controlled trials showed no large or clear differences for most outcomes between TAVI and surgery for adults with non-bicuspid AS, including mortality outcomes and quality of life".	Thank you for your comment. We have reviewed the meta-analysis that was cited and noted that it differs from the meta-analysis in evidence review H as it includes data up to 2 years, while evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Indeed, a recent meta-analysis by Siontis et al., 2019, focusing on the same 7 referred RCTs (except STACCATO trial and including Evolut Low Risk trial), and published in, concluded: "Compared with SAVR, **TAVI is associated with reduction in all-cause mortality and stroke up to 2 years irrespective of baseline surgical risk** and type of THV system". We propose the following statement: "Evidence from RCTs demonstrated that **TAVI is associated with reduction in all-cause mortality and stroke** up to 2 years **irrespective of baseline surgical risk** for adults with non-bicuspid AS. TAVI was also associated with a large improvement of quality of life."	outcomes). We note also that the risk ratios or hazard ratios did not suggest large differences between the two groups for many outcomes and the committee considered clinical importance of any differences as described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for most outcomes and the role health economic modelling had in the decision process. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					analysed separately because the invasiveness of surgery was unclear. The STACCATO trial remains included in the main analysis for the clinical review, as per the review protocol. However, this trial was not included in the economic modelling based on the transapical access route not being in line with current practice.
Edwards Lifesciences	Guideline	036	003 - 026	Rational why the committee made the recommendations. AS when surgery is suitable. In this section, we believe **critical evidence have been disregarded and/or misinterpreted**. We would like to raise our concerns on the evidence missing that would give another view on the positioning of TAVI versus surgery. On top of the evidence, we would like to also inform NICE about **recent positive HTAs acknowledging TAVI (and SAPIEN 3) superiority vs. surgery for low-risk patients with sSAS** (France (HAS 2020), Norway (NIPH 2021), Ireland (HIQA 2019), Canada (Ontario Health 2019 and 2020). We will go into more details in the Evidence Review H: Intervention section but would also bring in this section a specific meta-analysis by **Siontis et al., 2019**, **focusing on RCTs only** and published in the European Heart Journal.	Thank you for your comment. We have reviewed the meta-analysis that was cited and noted that it differs from the meta-analysis in evidence review H as it includes data up to 2 years, while evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes). All meta-analyses that were excluded were checked as a source of references for included studies that would also be relevant to our review, and outcomes

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Given the technological advancements and procedural improvements in TAVI over the past decade, we believe it is important to assess study outcomes in the context of the devices used and the study period. In this regard, we believe that 3 dimensions should not be pooled but looked at separately: 1. **TAVI major improvements with latest generation of devices** There is a large body of evidence demonstrating the improvements of outcomes with the valve's generation. A recent meta-analysis published in NATURE Scientifc Research (Winter et al., 2020) addressed "**TAVR with contemporary next generation devices has led to an impressive improvement in TAVR safety** driven by refined case selection, improved procedural techniques and increased site experience." We are concerned that **most of the evidence used is not based on the latest technology currently in use in the UK**. An example is SAPIEN 3 balloon expandable valve, which was launched in 2014 already; only one RCT (PARTNER 3 trial) has been considered (low-risk patients using transfemoral approach) within this draft guidance. We believe a 2021 Guidance on HVD should reflect current practice and shall not be influenced negatively by first-generation technology and/or evidence that would not reflect current practice. 2. **Transfemoral Approach representing 95%+ of all TAVI interventions.**	extracted according to our review protocol. The design of the review in terms of pooling and stratification were discussed at length with the committee during the development of the review protocol. It was agreed that studies comparing transcatheter intervention with surgical intervention would be combined initially, regardless of factors such as device generation and TAVI approach. However, it was agreed that for any outcomes where heterogeneity was present in the meta-analysis, the impact of certain factors that were thought most likely to have an effect on outcome (including access route and operative risk, for example) on the outcome would be explored using subgroup analyses. Device generation and balloon- vs. self-expandable valves were not subgroup strategies that were prespecified in the protocol.7

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Transfemoral approach is the preferred approach and is also a critical criterion in the latest guidelines favouring TAVI vs. surgery. Early trials were mixing transfemoral with other type of approach (transapical, subclavian, transthoracic, etc.). In the Siontis 2019 meta-analysis, we clearly see the difference between the 2 approaches as: • Transfemoral favouring TAVI: pooled HR = 0.83 with 95% CI [0.72 – 0.94] • Transthoracic favouring Surgery (not statistically significant thought): pooled HR = 1.17 with 95% CI [0.88 – 1.55] Another example is our PARTNER 3 trial for low-risk patients: only transfemoral access route was used, other routes were excluded. **3. Different type of TAVI Valve (balloon expandable vs. self-expandable)** We would also like to stress that there are **important differences** for certain outcomes **between balloon-expandable valves** (SAPIEN family) and **self-expandable valves** (CoreValve Evolut, Portico, Accurate NEO, etc.). The best example is the risk of permanent pacemaker implantation – which differ dramatically between the 2 type of TAVI device[ix,xxiv,xxv,xxvi,xxvii,xxviii,xxix,xxx] (see comments #28 and #39 below)	Following further committee discussion, it was agreed to use in the base case scenario relative treatment effects estimated from trials evaluating only 2nd and 3rd generation valves (PARTNER 2, PARTNER 3 and Evolut) to account for recent technological improvements. These are predominantly on the transfemoral approach. The analysis was undertaken with the goal of assessing whether TAVI was cost-effective compared to surgery, therefore evidence on balloon expandable and self-expandable valves were pooled together.
Edwards Lifesciences	Guideline	036	005 - 007	Rational why the committee made the recommendations. AS when surgery is suitable.	Thank you for your comment. We have reviewed the meta-analysis that was cited and noted that it differs from the meta-analysis in evidence

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In the same meta-analysis by Siontis et al., 2019[ix],, some additional significant benefits for TAVI vs. surgery are demonstrated with the following secondary outcomes: • Acute kidney injury (pooled HR = 0.56 with 95% CI [0.38 – 0.81]) • New onset of AF (pooled HR = 0.34 with 95% CI [0.23 – 0.51] • Major Bleeding (with pooled HR = 0.46 with 95% CI [0.31 – 0.69]) We suggest changing the following sentence: "However, a benefit of TAVI was identified for major bleeding and atrial fibrillation at 30 days, and length of hospital stay after the intervention. Absolute effects for other outcomes also suggested a benefit, but there was more uncertainty based on the confidence intervals." With: "Moreover, a benefit of TAVI was identified for **acute kidney injury**, major bleeding and atrial fibrillation at 30 days, and length of hospital stay after the intervention." Absolute effects for other outcomes also suggested a benefit, but there was more uncertainty based on the confidence intervals."	review H as it includes data up to 2 years, while evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes). All meta-analyses that were excluded were checked as a source of references for included studies that would also be relevant to our review, and outcomes extracted according to our review protocol (see Appendix A).
Edwards Lifesciences	Guideline	036	009	Rational why the committee made the recommendations. AS when surgery is suitable. If we agree with your statement that overall, there is a harm of TAVI for pacemaker implantation at 30 days, it cannot be generalized to all TAVI devices. To give more precise and granular recommendation we ask for a clear distinction between balloon-expandable and self-expandable TAVI devices.	Thank you for your comment. The design of the review in terms of pooling and stratification were discussed at length with the committee during the development of the review protocol. It was agreed that studies comparing transcatheter intervention with surgical intervention

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				As reported by Winter 2020[xxxv]: "Need of PPI is still highly attributable to **the expansion system**", and in Siontis 2019[ix] the permanent pacemaker implantation up to 2 years follow-up differ significantly between the transcatheter heart valve system versus surgery: • Balloon-expandable: pooled HR = 1.23 with 95% CI [0.99 – 1.52] – not statistically significant • Balloon-expandable with SAPIEN 3 in the PARTNER 3 trial: HR = 1.38 with 95% CI [0.82 – 2.32] – not statistically significant • Self-expandable: pooled HR = 3.44 with 95% CI [2.27 – 5.20] – highly statistically significant Therefore, we propose the following wording: "Overall, a harm of TAVI was identified for pacemaker implantation at 30 days. **However, we stress that the risk is highly dependent on the type of TAVI device used, with a major increased risk linked to the use of self-expandable devices**."	would be combined initially, regardless of factors such as device generation and TAVI approach. However, it was agreed that for any outcomes where heterogeneity was present in the meta-analysis, the impact of certain factors that were thought most likely to have an effect on outcome (including access route and operative risk, for example) on the outcome would be explored using subgroup analyses. Balloon- vs. self-expandable valves were not subgroup strategies that were prespecified in the protocol because the committee did not highlight this as a potential source of heterogeneity and therefore evidence could not be considered separately for these two types of valves.
Edwards Lifesciences	Guideline	036	010-013	Rational why the committee made the recommendations. AS when surgery is suitable. "Although absolute effects also suggested a possible harm of TAVI in terms of mortality, need for reintervention, rehospitalisation and major vascular complications, the direction and size of the effect was much more uncertain	Thank you for your comment. We note that the risk ratios or hazard ratios did not suggest large differences between the two groups for many outcomes but the committee considered any difference in mortality

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				for these outcomes and no clear difference between the 2 groups could be identified." We suggest removing the mortality component as we clearly see some benefits in terms of early mortality with TAVI (comment #25 above). Regarding need for reintervention, we might want also to be careful about the type of device and the generation considered. Recently SAPIEN 3 device was followed up to 5 years and compared to surgery for the intermediate risk patients (PARTNER 2 S3i cohort) using the latest VARC-3 criteria (Pibarot 2020)[xiv]. In this publication published in JACC (Impact factor = 20.6) the authors concluded "Compared with SAVR, the second-generation SAPIEN XT balloon-expandable valve has a higher 5-year rate of SVD, **whereas the third-generation SAPIEN 3 has a rate of SVD that was not different from SAVR**". Regarding re-hospitalisation, this is clearly a benefit favouring TAVI with SAPIEN 3 in our latest PARTNER 3 trial (Mack 2019 and Leon 2021): • At 1 year follow-up: 7.3% vs. 11.3% for TAVI and surgery respectively w. HR [95%CI] = 0.63 [0.41-0.97] • At 2-year follow-up: 8.5% vs. 12.5% for TAVI and surgery respectively w. HR [95%CI] = 0.67 [0.45 – 1.00] Regarding major vascular complication, again it was quite clear in the early days that TAVI was associated with an increased risk due to larger transcatheter diameter. However, with the improved technology and the reduced catheter diameter the incidence of major vascular complication	based on the absolute risk difference to be important. This is described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for most outcomes and the role health economic modelling had in the decision process. The point about need for re-intervention possibly reducing with more contemporary valves was discussed with the committee and incorporated into the discussion section of the evidence review. The design of the review in terms of pooling and stratification were discussed at length with the committee during the development of the review protocol. It was agreed that studies comparing transcatheter

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				has been reduced significantly. Both in Winter 2020 and Siontis 2019 we can see the improvement and in our latest PARTNER 3 trial with SAPIEN 3 there is no statistically significant difference at 30 days or 1 year (2.2% vs. 1.5% at 30 days and 2.8% vs. 1.5% at 1y). Therefore, we suggest the following sentence – ensuring it reflects latest evidence with current device in use: "Although previous generations of TAVI valve demonstrated a higher incidence for need for reintervention, rehospitalisation and major vascular complications, these events were significantly reduced, and the effect reversed with the latest technology currently in use."	intervention with surgical intervention would be combined initially, regardless of factors such as device generation. However, it was agreed that for any outcomes where heterogeneity was present in the meta-analysis, the impact of certain factors that were thought most likely to have an effect on outcome (including access route and operative risk, for example) on the outcome would be explored using subgroup analyses. Device generation was not one of the factors included as a subgrouping strategy and therefore clinical evidence could not be considered separately for this factor.
Edwards Lifesciences	Guideline	036	014	Rational why the committee made the recommendations. AS when surgery is suitable. "Only 1 study reported data beyond 5 years, but only for all-cause mortality." It is correct and was defined per-protocol. We would like to inform the Committee that the current PARTNER 3 trial comparing SAPIEN 3 vs. surgery for low risk sSAS patients is planned to have a 10-year follow-up to address the durability question.	Thank you for your comment. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Edwards Lifesciences	Guideline	036	018 - 021	Rational why the committee made the recommendations. AS when surgery is suitable. "The results of the health economics model showed that TAVI was not cost effective when surgery was also an option. This applied to people at low, intermediate, and high risk for surgery and for different age groups." We completely disagree with NICE findings which are not aligned with what has been published in the literature. We strongly believe also that mixing types of devices, generation of devices, access route and indications preclude a clear picture of the situation from a health economics perspective. Recently, many studies have been published in the literature (Tam 2020, Zhou 2020) or HTAs (Ireland (HIQA), France (HAS), Norway (NIPH, Canada (Ontario Health)) demonstrating that TAVI with the SAPIEN 3 device was actually dominant versus surgery for the low-risk patients, with cost savings driven by reduced complication rates and shorter hospitalization. We do know from the literature that surgery performs best for these low-risk patients, which means that for intermediate and high-risk patients SAPIEN 3 would be even more cost-effective. We also have a full body of evidence demonstrating this: • SAPIEN 3 cost-effectiveness for IR: Baron 2019, Goodall 2019, Zhou 2019, Tarride 2019 and Pinar 2021 SAPIEN 3 cost-effectiveness for HR: Tarride 2019 and Pinar 2021.	Thank you for your comment. The model was revised to use only contemporary data reflecting current practice and costs. We think that the current version of the model is reflecting outcomes and costs in the NHS. The results of the economic analysis are consistent with previous cost-effectiveness analysis: High risk ICER: • NICE model: £14,000 • Tarride 2019 (Canada): £9,510 (they used a cheaper price for TAVI) Intermediate risk ICER: • NICE model: £50,000 • Kodera 2018 (Japan): £51,210 • Tam 2018 (Canada): £43,055 • Goodall (2019) found that TAVI dominates SAVR but their analysis is using French prices for valves which are

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					priced much lower than the ones in the UK. To give an example, a Sapien 3 valve in France is charged around £12,000 (source: https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036577833) whereas the average price of a TAVI valve in the UK is £17,500 (source: NHS Supply Chain). At this price, the NICE model reaches the same conclusion of Goodall • Tarride 2019: £15,500. Though they use a cheaper price for the valve as in Canada Sapien 3 is charged less (£14,500). At the same price, the NICE model assesses TAVI to be cost effective as well. Low risk ICER: • NICE model: £136,000 • Tam 2018: £15,900 but they used Canadian price for Sapien 3 (£14,500). At the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					same price the NICE model assesses TAVI to be cost effective in low risk patients as well. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Guideline	036	021 - 022	Rational why the committee made the recommendations. AS when surgery is suitable. "The committee agreed that if surgery is an option, it should be offered to those with severe aortic stenosis requiring intervention." We believe that surgery is an option but not the only one. We suggest here to be less categorical and propose both options based on the	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				multidisciplinary team decision. Therefore, we suggest the following sentence: "The committee agreed that if any intervention (surgery or TAVI) is an option, it should be offered to those with severe aortic stenosis. Depending on age and anatomic contraindication, either surgery of transfemoral TAVI is recommended after **shared decision making between the patients and the multi-disciplinary heart team** (MDT) about the balance between expected patient longevity and valve durability."	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention. Recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Edwards Lifesciences	Guideline	036	024 - 026	Rational why the committee made the recommendations. AS when surgery is suitable. "…because suitability of surgery does not depend on the type of aortic stenosis. TAVI is also considered to be more difficult in bicuspid aortic stenosis." We would like to stress that latest generation of TAVI valves demonstrated excellent results also for patients with bicuspid valves. Indeed, for patients with bicuspid valve, we do have strong evidence from real world practice demonstrating that TAVI is as good as for tricuspid valve (Halim et al 2020[Error! Bookmark not defined.] and Makkar et al[Error! Bookmark not defined.]) – ensuring "*TAVI is a viable treatment option for patients with bicuspid AV disease*".	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the evidence. In addition, the committee noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated in this area was not prioritised for a research recommendation for the same reasons.
Edwards Lifesciences	Guideline	042	005	We do acknowledge that the most robust scientific evidence comes from RCT, but we believe that real-world evidence (RWE) is also needed to justify the transposability of the clinical data into the real clinical practice.	It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Hence, **we would like to promote the consideration of RWE available on TEER** suggesting that a greater reduction in MR severity with TEER: • is associated with a greater left ventricular and left atrium reverse remodelling, a clinical improvement (change of New York Heart Association (NYHA) class, increased 6-min walking distance) [3-6]. • and improved survival [7-9]. [3] Adamo M. et al. Left ventricular reverse remodelling predicts long-term outcomes in patients with functional mitral regurgitation undergoing MitraClip therapy: results from a multicentre registry. Eur J Heart Fail 2018;21:196–204. 2018 ; [4] Geis NA et al. Safety and efficacy of MitraClipTM therapy in patients with severely impaired left ventricular ejection fraction: results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail 2018;20:598–608. 2018 ; [5] Neuss M et al. Patient selection criteria and midterm clinical outcome for MitraClip therapy in patients with severe mitral regurgitation and severe congestive heart failure. Eur J Heart Fail 2013;15:786–795.; [6] Nickenig G et al. Transcatheter Valve Treatment Sentinel Registry Investigators of the EURObservational Research Programme of the European Society of Cardiology. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. J Am Coll Cardiol 2014;64: 875–884. [2]	(i.e., bridge the efficacy/effectiveness gap). However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. Real world evidence may be considered if no or limited RCT evidence had been found, but in this instance RCT evidence was available. Whilst broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap), it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. Cohort studies were not included also for this reason and for the difficulty of controlling for confounders.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[7] Swaans MJ et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. JACC Cardiovasc Interv 2014;7:875–881. 2014. [8] Velazquez EJ et al. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: a propensity-matched comparison. Am Heart J 2015;170:1050–1059.e3. [9] Giannini C et al. Comparison of percutaneous mitral valve repair versus conservative treatment in severe functional mitral regurgitation. Am J Cardiol 2016;117:271–277.	
Edwards Lifesciences	Guideline	042	012	As described in the ACC / AHA guideline, the outcomes discrepancy between COAPT (Stone G.W. *et al.* 2018) and MITRA-FR (Obadia J.F. *et al.* 2018) trials may be explained by the difference between patients' baseline characteristics in the trial. Indeed, MITRA-FR enrolled patients with greater degrees of left ventricular enlargement and less severe MR (mean effective regurgitant orifice area (EROA) of 0.31 cm2 versus 0.41 cm2). In addition, the inclusion criterion in MITRA-FR of a left ventricular end systolic diameter (LVESD) up to 70 mm represents extreme dilation; in contrast, in the COAPT trial, the mean LVESD was smaller (52±9 mm), and even the left ventricular end diastolic diameter (LVEDD) rarely exceeded 70 mm (mean 62±7 mm). Thus, the enrolment criteria in COAPT trial (left ventricular ejection fraction between 20% and 50%, LVESD ≤70 mm, pulmonary artery systolic pressure ≤70 mm Hg, and persistent symptoms (NYHA) class II, III, or IV] while on optimal GDMT) are the current standard selection criteria for TEER for secondary MR.	Thank you for your comment. The economic analysis was based on COAPT population who are characterized by a more severe form of MR if compared with people enrolled in the MITRA-FR. The analysis found MitraClip to be above the £30,000 threshold and therefore medical management was recommended to people with severe secondary MR (although the procedure is still considered if symptoms do not improve). As recognized by Edwards Lifesciences, COAPT-like patients are more likely to have a better prognosis after an edge-to-edge mitral valve repair. Therefore,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In addition, a recent real-world study [10] has shown that compared with non-COAPT-like patients, those fulfilling COAPT criteria had greater survival free from all-cause death and from the composite endpoint at both 2-year (75% vs. 55% and 67% vs. 47%; p < 0.001 for both) and 5-year (49% vs. 25% and 40% vs. 19%; p < 0.001 for both) follow-up. Among the non-COAPT-like patients, similar outcomes were observed in those fulfilling 1 or ≥ 1 criterion. The author concludes that a COAPT-like profile, including specific echocardiographic and clinical criteria, identifies patients with secondary MR who have a better prognosis after transcatheter edge-to-edge repair. Hence, we suggest **adding a clear distinction between COAPT-like and MITRA-FR like patients and consider a distinct recommendation for each patient profile**. [10] Adamo M et al. COAPT-Like Profile Predicts Long-Term Outcomes in Patients With Secondary Mitral Regurgitation Undergoing MitraClip Implantation. JACC Cardiovasc Interv 2021;14:15-25.	if the model did not find the procedure to be cost effective in a COAPT-like population, it is unlikely that it would be cost effective in people with less severe MR or with MITRA-FR characteristics. Hence, there is no need for a different recommendation as recommendation 1.5.13 is valid for people with MITRA-FR or COAPT characteristics alike.
Edwards Lifesciences	Guideline	042	012	The guideline does not include the latest 3-year follow-up of COAPT trial [11] showing that TEER is associated with: • sustained 3-year improvements in mitral regurgitation severity, quality-of-life measures, and functional capacity, • a fewer annualized rates of heart failure hospitalizations per patient-year compared to GDMT alone (35.5% vs. 68.8%; hazard ratio [HR]: 0.49; 95% confidence interval [CI]: 0.37 to 0.63; p < 0.001), • a reduced mortality compared to GDMT (42.8% versus 55.5% ; HR: 0.67; 95% CI: 0.52 to 0.85; p = 0.001).	Thank you for your comment. The latest 3-year COAPT follow-up was added to the evidence and the MitraClip model was updated accordingly to reflect the new parameters. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Moreover, among 58 patients assigned to GDMT alone group who crossed over and were treated TEER, the subsequent composite rate of mortality or heart failure hospitalizations was reduced compared with those who continued GDMT alone (adjusted HR: 0.43; 95% CI: 0.24 to 0.78; p = 0.006). We suggest considering these data in the guideline. [11] Mack MJ et al. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure. J Am Coll Cardiol 2021;77:1029-1040.	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Edwards Lifesciences	Guideline	043	022	The guideline does not consider the preliminary clinical data available on tricuspid TEER. Indeed, 2 prospective single-arm studies and 1 compassionate cases experience have been published and show the potential benefits of these transcatheter therapies: • The CLASP TR early feasibility study [12] shows that at 30 days, 85% of patients treated achieved a tricuspid regurgitation (TR) severity reduction of at least 1 grade, with 52% with moderate or less TR (p<0.001). The major adverse event rate was 5.9%, and none of the patients experienced cardiovascular mortality, stroke, myocardial infarction, renal complication, or reintervention. Eighty-nine percent of the patients improved to NYHA functional class I/II (p< 0.001), the mean 6-min walk distance improved by 71 m (p < 0.001), and the mean Kansas City Cardiomyopathy Questionnaire (KCCQ) score improved by 15 points (p < 0.001). The authors conclude that in this	Thank you for your comment. Evidence review H included RCTs comparing interventions specified in the review protocol in Appendix A, while the studies mentioned in your comment are non-randomised, with many being non-comparative, single-arm studies allowing no comparison between two different interventions. The committee has now made consensus recommendations on interventions for tricuspid valves (1.5.14 and 1.5.15).

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				preliminary study, the PASCAL repair system performed as intended, with substantial TR reduction, favourable safety results with a low major adverse events rate, no mortality or reintervention, and significant improvements in functional status, exercise capacity, and quality of life. • In addition, the compassionate cases experience on PASCAL repair system [13] corroborates the CLASP TR EFS findings showing that moderate or less TR was achieved in 82% of patients at 30 days, which was sustained at 12 months (86%). One-year survival rate was 93%. NYHA functional class I or II was achieved in 90% and 6-minute walk distance improved from 275 ± 122 m at baseline to 347 ± 112 m at 12-month (increase of 72 ± 82 m, p < .01). There was no stroke, endocarditis, or device embolization during the follow-up. • The TRILUMINATE trial [14] shows longer follow-up results with at 1 year a TR reduced to moderate or less in 71% of subjects compared with 8% at baseline (p < 0.0001). Patients experienced significant clinical improvements in NYHA functional class I/II (31% to 83%, p < 0.0001), 6-minute walk test (272.3 ± 15.6 to 303.2 ± 15.6 meters, p = 0.0023) and KCCQ score (improvement of 20 ± 2.61 points, p < 0.0001). Significant reverse right ventricular remodelling was observed in terms of size and function. The overall major adverse event rate and all-cause mortality were both 7.1% at 1 year.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				[12] Kodali S et al. Feasibility study of the transcatheter valve repair system for severe tricuspid regurgitation. J Am Coll Cardiol. 2021 Feb 2;77(4):345-56. [13] Kitamura M, Fam NP, Braun D, Ruf T, Sugiura A, Narang A, Connelly KA, Ho E, Nabauer M, Hausleiter J, Weber M, Nickenig G, Davidson CJ, Thiele H, von Bardeleben RS, Lurz P. 12-Month outcomes of transcatheter tricuspid valve repair with the PASCAL system for severe tricuspid regurgitation. Catheter Cardiovasc Interv. 2021 Mar 4. doi: 10.1002/ccd.29583. Epub ahead of print. PMID: 33660364. [14] Lurz P et al. Transcatheter Edge-to-Edge Repair for Treatment of Tricuspid Regurgitation. J Am Coll Cardiol. 2021 Jan 26;77(3):229-239.	
Edwards Lifesciences	Guideline	General	General	The following are the key general areas of comment on this draft guideline and are addressed in more detail in subsequent comments: • The intervention recommendations do not reflect current clinical practice and the latest medical guidelines. • The role of the multidisciplinary Heart Team in deciding the most appropriate treatment for the patient is not made the focus in the intervention section whereas this is the case in all national and international guidelines. The Heart Team should be stated clearly as the decision maker of the patient's intervention and guidance should be included as in the current guidelines to assist with this decision. • The distinction between mechanical and bioprosthetic surgical valves and also balloon expandable and self-expandable Transcatheter Aortic Valve Implant (TAVI) valves should made in the draft guideline.	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

				• The draft guideline refers to the NICE TAVI Interventional Procedure Guidance (IPG) (2017) that is inconsistent with recent positive conclusions in TAVI Health Technology Assessment (HTA) reports from other countries (i.e. France (Haute Autorité de Santé (HAS) 2020), Norway (Norwegian Institute of Public Health (NIPH) 2021), Ireland (Health Information and Quality Authority (HIQA) 2019), Canada (Ontario Health 2019 and 2020)).
				• Evidence considered for the review are very partial and in particular the following;
				  ○ Based on legacy products no longer on the market – not considering the iterative nature of the technologies and consequent evidence
				  ○ The review was limited to Randomized Controlled trials (RCTs) only (meta-analysis and observational studies excluded); hence critical evidence has been disregarded – this is counter to the objectives in the recently published NICE 5 Year Strategic Plan
				  ○ Patients' preferences and Quality of Life (QoL) considered very partially in the evidence review: the risks associated with the procedure for the various procedure options (both TAVI or surgery) should be mentioned for a sound decision making for the patients.
				• Secondary (Functional) Mitral Regurgitation (MR) – The indication for Transcatheter edge-to-edge repair (TEER) for secondary MR does not reflect the latest recommendations from medical societies and from the joint position statement as well as latest available clinical data.
					MDTs as an example of how this may be provided.
					
					Type of valve was a subgroup in the review protocol (see appendix A evidence review H). However, this subgrouping strategy did not explain any heterogeneity that was found in the meta-analyses and no recommendations could therefore be made by the committee regarding biological and mechanical valves. In terms of self-expanding TAVI valves, this was not pre-specified in the protocol as a subgrouping strategy to use if heterogeneity was observed.
					
					Study designs to be included in each review were discussed with the committee during the development of each review protocol and for this review there was considered to be enough RCT evidence, with no concerns about much of this evidence being from older generation devices raised. Therefore, non-randomised studies were not prioritised for this

Stakeholder	Document	Page No	Line No	Comments	Developer's response

				• Specific consideration for the COVID-19 pandemic needs to be incorporated into the draft guideline - recommendations from the national and European scientific societies to use minimally invasive interventions to protect clinical services and clear the elective backlog.
				• TAVI Cost-effectiveness:
				  ○ Evidence review (incl. HTAs) not exhaustively considered
				  ○ Very heterogeneous evidence plugged into the model – mixing TAVI devices, TAVI generation devices, access routes and indications.
				  ○ Costs of the valve and the procedure are incorrect
				  ○ Many of the model parameters are not based on current evidence
					review. However, in the economic model, a different meta-analysis based on trials evaluating 2nd and 3rd generation valves was used to estimate treatment effects. This was done after a further discussion with the committee which highlighted the importance of capturing recent efficiency improvement in the economic analysis.
					
					The importance of shared decision-making and discussion of risks and benefits has been emphasised in the recommendations under 'decisions about interventions, with reference to shared decision-making as part of the NICE guideline on patient experience in adult NHS services made.
					
					NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account. The model demonstrated that transcatheter mitral valve repair had a low chance of being cost effective at £20,000 per QALY gained, with an incremental cost-effectiveness ratio of £30,000 per QALY gained. These results are in line with the UK study identified in the literature review. The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI cost-effectiveness: HTAs and other economic evidence were considered but largely assessed to be not applicable to the NHS case as often based on different assumptions on the price of the valve. The model was revised to use only latest generations devices using predominantly the transfemoral approach. Costs were recalculated as well and are in line with the costs provided by several Trusts (around £5,500).
Edwards Lifesciences	Other	General	General	Specific **considerations related to COVID-19 pandemic** to be taken into account: COVID-19 pandemic added a dramatic **burden on healthcare resources and facilities hindering the access to timely care for cardiovascular diseases.** Considering the life-threatening nature of severe symptomatic aortic stenosis (sSAS), many scientific societies have issued adapted specific recommendations on the management of cardiovascular diseases, including sSAS. In this specific context, the calls from the European (ESC Position 2020) and national (Recommendations from the ACI-SEC 2020) societies including the ones from the UK (British Cardiovascular Society/ British Cardiovascular Intervention Society (BCS/BCIS) 2020; NHS England and NHS Improvement), recommended to reconsider the balance	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				towards the **use of minimally invasive transfemoral TAVI (when feasible) as an alternative to surgery for intermediate and low-risk patients.** The use of **SAPIEN 3™** balloon expandable valve helps: 1) optimize the hospital resource utilization – by avoiding general anaesthesia and intubation, shortening (or preventing) Intensive Care Unit (ICU) stay, and accelerating hospital discharge and recovery, 2) foster adequate patients' prioritization, 3) address patient preferences and 4) **maintain the highest standard of care** for urgent cases like COVID-19 patients. Specific considerations related to COVID-19 pandemic to be considered as well for mitral and tricuspid regurgitations: The use of **PASCAL repair system** helps: 1) optimize the hospital resource utilization by shortening (or preventing) ICU stay, and accelerating hospital discharge and recovery, 2) foster adequate patients' prioritization, 3) address patient preferences and 4) **maintain the highest standard of care** for urgent cases like COVID-19 patients.	
Guy's and St Thomas' NHS Foundation Trust	Guideline			Part 1.3.8 What is the evidence of surgery in severe MR based on LVSDi 22mm? The advice about the estimated PA pressure at rest is not clear. Does this say that a PA pressure > 50 mmHg at rest is an indication for surgery? Is this guideline saying that asymptomatic patients with non-repairable mitral valves should have surgery? The large difference in risk between repair and replacement has not been taken adequate account of. Repairability needs to be the first step in the assessment at this stage.	Thank you for your comment. LVSDI recommendation was based on two studies, one showing increased onset of symptoms/LV dysfunction and the other showing increased congestive heart failure, LV dysfunction or death.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					See the committee's discussion of the evidence in evidence review D. The recommendation suggests PA pressure at rest >50 should be taken into account when deciding if there is an indication for surgery but the evidence was not strong enough to include as stand alone indicator
Guy's and St Thomas' NHS Foundation Trust	Guideline			Part 1.4.1 How does discussion with the patient affect the frequency of visits. How does the echocardiogram affect this decision, is this based on the peak velocity?	Thank you for your comment. Clinical practice regarding the frequency of follow up is highly variable and the committee were unable to be more specific but identified the factors that should be considered. These include how stable the patient has been over previous years, how confident you are about the patient degree of symptoms, and how close the echocardiographic parameters are to the thresholds that might indicate intervention. There is a wide range of variety in this, which is why a flexible approach as judged by the treating cardiologist and the patient is recommended.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Guy's and St Thomas' NHS Foundation Trust	Guideline	004		Part 1.1.2 Peripheral oedema is listed as a significant sign of valve disease but this is a common finding usually caused by incompetent veins or being overweight. It only occurs in end-stage left-sided valve disease or in the presence of severe decompensating tricuspid regurgitation when systolic waves in the neck or a pulsatile liver will be far more specific signs.	Thank you for your comment. Peripheral oedema is not listed as a significant sign of valve disease, but as a finding in need of further evaluation by echocardiography.
Guy's and St Thomas' NHS Foundation Trust	Guideline	004	004	Part 1.1.1 Many patients do not have a murmur and valve disease is also detected by offering TTE to patients with atrial fibrillation. First degree relatives of probands with a bicuspid aortic valve also have an approximately 10% chance of having a bicuspid valve and should be offered TTE. Breathlessness should include patients with COPD and disproportionate breathlessness and a raised BNP level.	Thank you for your comment. Recommendation 1.1.1 now refers to atrial fibrillation. The recommendation focuses on people in who heart valve disease is suspected which would not apply if the person was breathless due to COPD. BNP is referred to in section 1.3 on indications for interventions. First degree relatives of people with bicuspid aortic valve are also now referred to in the committee's discussion of the evidence in evidence review A.
Guy's and St Thomas' NHS Foundation Trust	Guideline	005	002	Part 1.1.3 What is meant by 'consider urgent assessment for patients with a murmur and breathlessness or angina on minimal exertion or at rest'? Does this mean a referral to A and E? Chest pain at rest suggests an acute coronary syndrome rather than valve disease and should certainly receive immediate emergency attention.	Thank you for your comment. Recommendation 1.1.3 has been edited and now refers to severe symptoms thought to be related to heart valve disease.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Guy's and St Thomas' NHS Foundation Trust	Guideline	005	020	Part 1.1.7 Patients with mitral prolapse should be offered a specialist review if they have a cardiac arrhythmia. What about if they have mitral regurgitation? Should all patients with mitral prolapse, approximately 2-4% of the population, have 24 hour tapes?	Thank you for your comment. The example you give would be included in the recommendation 1.1.7. The use of 24 hr tapes was not included in the scope of this guideline
Guy's and St Thomas' NHS Foundation Trust	Guideline	006	008	Part 1.1.8 Discussion about contraception and family planning are important at the outset as soon as significant valve disease is diagnosed.	Thank you for your comment. We have made new recommendations 1.1.9 and 1.1.10 to emphasise the importance of contraception and family planning
Guy's and St Thomas' NHS Foundation Trust	Guideline	006	010	Part 1.1.9 Not just the type of replacement heart valve needs to be discussed but also the timing of surgery in relation to family planning in general.	Thank you for your comment. We have made new recommendations 1.1.9 and 1.1.10 on contraception and family planning.
Guy's and St Thomas' NHS Foundation Trust	Guideline	007	003	Part 1.2.1 It would help to have a recommendation about the use of statins here rather than the need to access another document	Thank you for your comment. There was no evidence to suggest a benefit for statins except for overall cardiovascular health. The recommendation cross-referring to the NICE guideline on statins has been removed. As current clinical practice is variable the committee agreed to

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					make research recommendations to promote further research in this area.
Guy's and St Thomas' NHS Foundation Trust	Guideline	007	007	Part 1.2.2 Patients with mitral stenosis and heart failure usually need surgery. A beta-blocker is a bridge to surgery or for patients in whom surgery is contraindicated.	Thank you for your comment. The recommendation does not preclude people with mitral stenosis and heart failure having surgery.
Guy's and St Thomas' NHS Foundation Trust	Guideline	008	006 - 007	Assessment and suitability for intervention should be determined by a multidisciplinary heart team which acts in the patient's best interests.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided
Guy's and St Thomas' NHS Foundation Trust	Guideline	009	004	Part 1.3.6 What is the evidence for surgery in AS for mid-wall fibrosis on MRI in the absence of symptoms or a reduced LV EF? The committee discussion is balanced and reflects our cumulative experience but the recommendations appear to go beyond this evidence.	Thank you for your comment. Recommendation is for enhanced follow-up and not as an indication for intervention.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Guy's and St Thomas' NHS Foundation Trust	Guideline	011	004 - 012	A multidisciplinary approach should be encompassed within 'decisions about interventions.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Guy's and St Thomas' NHS Foundation Trust	Guideline	011	005	Part 1.5.1 Discussions about potential surgery need to start long before this is needed during the follow-up in the specialist valve clinic. The patient and cardiologist need to discuss indications for surgery, symptoms to look out for and types of intervention possible. This then allows the patient to think, look up information, discuss with their GP or friends, and plan their life. It means that informed consent occurs potentially over many years and not just at the point when surgery is needed. 'Valve durability' must mean durability of the replacement valve. This should be clarified. General point. The advice on repair vs replacement surgery vs transcatheter is not wrong but it is generalised and offers no insights to help clinical management. For example when is repair better than replacement for secondary mitral regurgitation?	Thank you for your comment. Recommendation 1.9.4 recommends that people are offered information and advice on the any need for intervention and this could occur at any stage in the patient pathway including long before a referral for intervention is made. We have clarified that we mean prosthetic valve durability (recommendation 1.5.1). When a repair is better than replacement for secondary mitral regurgitation was not identified as a

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Part 1.5.1 The committee appears not to have considered the evidence of subclinical leaflet thickening (HALT) which occurs usually early after implantation in some 5% of biological replacement valves and nearer 15% of TAVI. This may lead to early obstruction and responds to anticoagulation using vitamin K antagonists or NOAC. One theory for the lower incidence in replacement valves is that these have warfarin for 3 months as recommended in international clinical guidelines. This is an area of great uncertainty but does at least need to be considered. Should all patients after TAVI have a CT scan looking for early leaflet thickening? Probably not but this is being discussed and it would be useful to have the opinion of NICE.	priority review question by the committee. Leaflet thickening was not specified as an outcome in the review protocol (appendix A evidence review H). Outcomes were chosen by the committee based on their importance for decision making.
Guy's and St Thomas' NHS Foundation Trust	Guideline	012	003 - 007	Decisions concerning suitability for surgery or TAVI should be determined by a multidisciplinary heart team considering individual patient characteristics.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Guy's and St Thomas' NHS Foundation Trust	Guideline	015	010	Part 1.8.1 How is this list to be used to base decisions on follow-up frequency?	Thank you for your comment. In the absence of evidence and with current clinical practice variable it was not possible to specify a specific frequency of monitoring. The committee made a research recommendation. In the experience and opinion of the guideline committee all of the factors mentioned in 1.8.1 should be used to determine the frequency of monitoring. For example, a person with significant comorbidities may requires more frequent monitoring.
Guy's and St Thomas' NHS Foundation Trust	Guideline	016	013	Part 1.9.4 This section states that patients should be given information about how to access palliative care services. Surely a holistic valve clinic should help the patient with this?	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline.
Guy's and St Thomas' NHS Foundation Trust	Guideline	General	General	Heart valve disease is a heterogenous condition that does not readily lend itself to investigation by randomised trials. The NICE guideline approach based predominantly on the weight of large scale RCTs is therefore inapplicable. The document in its present format is therefore a huge disappointment to the UK clinical community, particularly given that the UK has made a major	Thank you for your comment. The different populations, if applicable, were defined by strata in the review protocols. In the presence of heterogeneity subgroups were used to explore possible reasons for this and included such factors as population

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				contribution in the past decade to the global evidence base underpinning the management of heart valve disease. The document is difficult to read and provides very little practical guidance for clinicians involved in the assessment and management of this challenging group of patients. The contrast with the "user friendly" yet evidence-based approach adopted by the ACC/AHA and ESC is stark. Inclusion of tables, flowcharts and diagrams would be of considerable additional value. Vague statements and throwaway recommendations for future research are both unhelpful and unrealistic. For example, "beta blockers may be considered in patients with mitral stenosis – further research is required". There will never be a clinical trial in this setting and the guidelines provide no recommendations concerning patient selection, rationale or treatment target. Recommendations for aortic valve intervention are way out of step with current clinical practice in the developed world. The number of TAVI procedures now comfortably exceeds the number of SAVR procedures in the UK, Europe and US, and the assumptions used to drive the NICE cost-effectiveness model (for example, use of ICU facilities and length of stay) are obsolete. There are many notable omissions: • The considerable progress with transcatheter valve intervention (particularly TAVI) in the past 10 years.	characteristics. See appendix A in the evidence reviews. The guideline committee discussed any evidence which showed different populations responded differently to the test or intervention and made recommendations accordingly. The online versions of the document contain hyperlinks which direct the reader from the recommendations to the rationale and impacts and also to the evidence reviews. Through user feedback NICE have found that this format is most useful for the reader. The guideline committee considered additional algorithms but the recommendations did not lend themselves to this format. The guideline committee considered that the beta blockers recommendation for mitral stenosis is feasible for example by a pragmatic RCT.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Factors determining the choice of intervention in younger low and intermediate risk patients with aortic stenosis. • The advantages of surgical mitral valve repair compared with mitral valve replacement. • The use of transcatheter intervention and cardiac resynchronisation therapy in secondary mitral regurgitation. • Details concerning the complexities of anticoagulant management – heart valve disease is not the same as AF and cross-reference to the AF guidelines is inappropriate. • Tricuspid valve disease. • Rheumatic fever prophylaxis. Risks of infective endocarditis in patients with heart valve disease (and its prevention).	We revised the economic model based on stakeholder comments to reflect contemporary costs and outcomes of modern valves (including the need of ICU facilities and LOS) but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk, although it became cost effective for high risk (1.5.3). Overall, the included evidence was limited; all studies were very small, with very few events reported for most outcomes and substantial uncertainty in the effects reported. Most outcomes were graded as very low quality. The lack of stronger evidence is likely to be because surgical repair has been preferred to replacement in mitral valve surgery for the past few decades based on observational evidence, and randomising to repair or replacement in those suitable for repair was thought to be unethical. Based on these limitations, the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					committee made recommendations reflecting current practice for those with severe mitral regurgitation requiring an intervention, with surgical repair recommended in those for whom it is suitable and replacement when repair is not suitable. Transcatheter intervention and cardiac resynchronisation therapy was not prioritised as an intervention in the review protocol for this question (appendix A evidence review H). The guideline committee considered the evidence for anticoagulation management and made recommendations based on the evidence. However, due to the limited evidence the guideline committee made research recommendations to inform any future update. One small study in people with atrial fibrillation suggested there may be no clear differences in outcomes between DOACs and vitamin K antagonists, and it is not common practice to use DOACs for this group. The committee agreed that if there is already an

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					indication for anticoagulation or antiplatelet therapy, for example, because of atrial fibrillation, the existing NICE guidelines for these indications should be followed. The committee have added recommendations on tricuspid regurgitation (1.5.14 and 1.5.15) Rheumatic fever prophylaxis and infective endocarditis were outside of the scope of the guideline.
Guy's and St Thomas' NHS Foundation Trust	Guideline	General	General	General point. The committee discussions are not adequately reflected in the guidance. For example the question of follow-up with mechanical replacement valves does not appear in the guidance. Follow-up can be useful to reduce the risk of endocarditis by ensuring that dental surveillance is being undertaken and the need for antibiotic prophylaxis before invasive dental procedures. It may be also pick up a new arrhythmia particularly atrial fibrillation in a patient with a biological valve which therefore leads to a significant change in management by initiating anticoagulation.	Thank you for your comment. The committee agree that follow up after intervention is important and we now highlight the issue you have raised in the committee's discussion of the evidence in evidence review H. The durability of the valve is a consideration when deciding on follow-up (recommendation 1.8.1).
Heart Valve Voice	Comments form	Q1		**1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** GP's need to listen to more hearts to bring diagnosis and treatment levels up to a point where it matches the prevalence of the condition. This would have a significant impact on workforce, but can be helped by adoption of digital stethoscopes which would empower more of the primary care	Thank you for your comment. The committee were confident that GPs and other non-cardiology specialists would have the skills necessary to identify the signs and symptoms covered by the recommendations.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				workforce to listen to hearts with better accuracy. From consultation we found that patients primary concern when having their heart listened to was 'accuracy', evidence has found that digital stethoscopes can listen to hearts with efficacy of 96%.	Digital stethoscopes were not included in the scope of this guideline.
Heart Valve Voice	Comments form	Q3		**3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)** - From consultation with 159 patients, we found that patients primary concerns when considering what they want from this guideline was "collaborative decision making' and 'patient choice.' Patients were involved in the methodology of our response, and we believe this level of engagement from patients would improve the design of guidelines and pathways. - Education at Primary Care level to improve the quality of stethoscope checks - Implementation of new technologies, such as digital stethoscopes, that will help support GPs, empower more primary care workers to listen to hearts with accuracy and increase the amount of hearts listened to. This will empower us to get the right patient to the right clinician at the right time. - National training and recruitment drive for echocardiography - Better access to minimal invasive surgery and transcatheter therapies across UK to drive down regional variation. - Standardised information given to all patients that is truly patient led. **4.** - National awareness campaign around symptoms of heart valve disease, specifically breathlessness.	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). Your comments will be considered by NICE where relevant support activity is being planned.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Heart Valve Voice	Comments form	Q4		**4. The recommendations in this guideline were largely developed before the coronavirus pandemic. Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.** At Primary Care, in-person services have been replaced with an increase in telemedicine, which has allowed practices to continue to see patients while limiting their exposure to Covid. This new style of appointment will likely continue, as it enables clinicians to see more patients. However, it has led to a fall in incidental diagnosis, which could lead to patients presenting later and sicker. Better investigation is required around red flag symptoms of breathlessness, dizziness and fatigue to ensure we continue to diagnose early. In addition to this, utilising innovative technologies, such as digital stethoscopes, can enable us to listen to more hearts with better accuracy and improve the speed and quality of referrals. It means up-skilling the workforce and empowering them with the skills and resources required to refer timely and efficiently. And it means innovating pathways, increasing opportunities to listen to hearts and improving processes to tertiary centres. Covid has also seen the fall in treatments, and increases in waiting lists. With waiting lists growing, we need to maximise opportunities to treat, including increasing use of minimal invasive and transcatheter procedures that result in shorter hospital stays and shorter recovery periods. This issue was highlighted in our recent JustTreatUs campaign, which reached over 10 million people through online, radio and TV media. Without addressing the issues above, it will likely lead to added stress to patients who have to wait longer for treatment.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned. We will pass your comment on digital stethoscopes onto the surveillance team at NICE for when this guideline is considered for update. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021 2. Silverman B, Balk M. Digital Stethoscope-Improved Auscultation at the Bedside. Am J Cardiol. 2019 Mar 15;123(6):984-985. 3. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	
Heart Valve Voice	Guideline	004	004 - 006	We are concerned that this recommendation may result in worse outcomes for patients. Evidence suggests that even patients with moderate or severe valve disease many present as asymptomatic, and therefore all patients who are found to have a murmur should be offered an echocardiogram. This recommendation may leave out opportunities to diagnose heart valve disease symptoms. Through consultation, we discovered that most heart valve disease patients were able to identify symptoms of breathless, dizziness and fatigue, in themselves, yet 40% did not receive a stethoscope check when they first presented with symptoms.This suggests a lack of awareness of heart valve disease at Primary Care level. Heart Valve Voice 'Primary Care Guidance states that "Echocardiography is indicated in any patient with a heart murmur if there is any suspicion of valve disease on clinical examination." A 2020 Heart Health Survey of over 60s found awareness of heart valve disease remains, with only 5.6% of people able to correctly describe what aortic stenosis was. The survey found that "Neither appointments with a GP driven by symptoms nor	Thank you for your comment. Limited evidence showed that murmur is an indicator of valve disease. But the evidence also showed that a substantial proportion of people with a murmur do not have valve disease confirmed by a reference test. The committee agreed that 'innocent' murmurs can occur, particularly during the teenage/young adult years and pregnancy. These are difficult to differentiate from pathological murmurs by clinical examination alone. The evidence was not strong enough to recommend that everyone with a murmur should be referred for echocardiography. The committee agreed that this would be a change in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				regular use of a stethoscope are a reliable guarantee for early diagnosis.", therefore timely referral to echocardiography should be prioritised for all patients who present with a murmur. It is our opinion that the language 'consider 'will lead to missed opportunities, later detection and worse outcomes. **References** 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021 2. Heart Valve Voice, Primary Care Guidance (2018), https://heartvalvevoice.com/application/files/8415/8436/2829/104_-_Practical_Guidance_FINAL.pdf, Accessed March 2021. Gaede, L, Sitges, M, Neil, J, et al. European heart health survey 2019. *Clin Cardiol*. 2020; 43: 1539– 1546. https://doi.org/10.1002/clc.23478	practice, would increase pressure on echocardiography services and would offer uncertain benefit.
Heart Valve Voice	Guideline	005	004 - 006	Urgent referral for specialist assessment or urgent echocardiography should happen in 2 weeks as per Heart Valve Voice's clinically approved Gold Standard of Care. Through consultation, we found 26% of patients were not told why they were waiting for an echo, which left them feeling 'anxious 'and 'scared.' Furthermore, 40% of patients asked in an online survey, reported waiting longer than 7 weeks for an Echo. In addition to this, our interactive webinar found 42% of patients waiting longer than 7 weeks, with some waiting as long as 6 months. 70% of patients who were referred for an echo, were given no information about what their murmur meant, which led to feelings of 'anxiousness',	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				however the majority felt 'reassured' and 'pleased to be under cardiologist care.' **References** 1. Heart Valve Voice, A Gold Standard in the Diagnosis,Treatment and Management of Heart Valve Disease in Adults (2019) Page 12. https://heartvalvevoice.com/application/files/9315/8436/2679/Gold_Standard__of_Care_For_Print.pdf Accessed April 2021 Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	
Heart Valve Voice	Guideline	005	017 - 019	We are concerned that this recommendation may result in worse outcomes for patients and increased stress and anxiety. Through our consultation, we found that patients felt 'relieved 'to be on a pathway, and 'calm 'and 'reassured' and 'pleased to be under cardiologist care.' Decisions on monitoring should be a shared decision between patients and clinician. Over 60% of patients felt information on their surveillance had been explained well, and 32% felt 'reassured', 35% confident and 35% calm. Surveillance and monitoring was seen to give patients comfort and confidence, making them reassured and safe and we believe the guidelines should reflect the patients wishes rather than pressures on workforce. **References** **1.** Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	Thank you for your comment. The committee have made a new recommendation to monitor people with mild to moderate valve disease every 3-5 yrs (1.4.2).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Heart Valve Voice	Guideline	010	014 - 018	We are concerned that this recommendation will result in worse outcomes and worse patient experience. Our consultation found patients prefer earlier treatment, with that 28.8% patients prioritising 'better outcomes if I'm stronger 'and 13% said delays in treatment would negatively effect their mental health. Decisions on when to treat should be a shared decision between patient and clinician and based on patient preference. Furthermore, the NHS Long Term Plan states that "Early detection and treatment of CVD can help patients live longer, healthier lives." We support this commitment to early detection and treatment of heart valve disease, and believe the guideline should do more to strengthen the Long Term Plan's commitment and the desires of patients. NICE Guidelines for 'Patient experience in adult NHS services: enabling patients to actively participate in their care' states clinicians should "openly discuss and provide information about the risks, benefits and consequences of the investigation or treatment options (taking into account factors such as coexisting conditions and the patient's preferences)" of treatment. With nearly a third of patients consulted prioritising the timing of treatment, we believe the guidelines should do more to reflect the want from patients to be treated earlier, which results in better outcomes. **References** 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021.	Thank you for your comment. In the experience of the committee follow-up between 6 and 12 months would identify the majority of people whose symptoms progress to necessitate treatment. The recommendations do not preclude more frequent monitoring based on individual clinical factors and discussion with the person. Recommendation 1.9.2 recommends that a point of contact for accessing specialist advice between appointments should be considered. This supports the person if they require advice between monitoring appointments.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. NHS Long Term Plan (2019(, Page 62, https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf, Accessed March 2021. NICE Guideline, Patient experience in adult NHS services: enabling patients to actively participate in their care, 2012, **https://pathways.nice.org.uk/pathways/patient-experience-in-adult-nhs-services/patient-experience-in-adult-nhs-services-enabling-patients-to-actively-participate-in-their-care#content=view-info-category%3Aview-about-menu,** Accessed April 2021.	
Heart Valve Voice	Guideline	011	005 - 012	We are concerned that this recommendation does not take into account the impact on the patients mental health, caring responsibilities or lifestyle. Through consultation we found that when making a decision on intervention, patients valued factors including mental health, lifestyle, work, family and caring responsibilities as well as symptoms. The discussion with the patient should include these factors to ensure optimal patient experience. In addition to this, when based on up to date evidence innovative treatments should be discussed on every Heart Team. Our consultation found that 27.2% of patients wanted treatment decisions to be based on most up to date evidence, and we feel the line "the type of access for surgery" should include transcatheter therapies. With a further online survey finding that 42% of patients valued their Heart Team and 'Up to date evidence' as central to decisions on treatment. Furthermore, the NICE Guideline on 'Patient experience in adult NHS services: enabling patients to actively participate in their care' states that	Thank you for your comment. Recommendation 1.9.1 is a cross reference to the NICE guidelines on patient experience which contains recommendations on taking into account the factors you describe (recommendations 1.1 knowing the patient as an individual). The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				clinicians should "Accept and acknowledge that patients may vary in their views about the balance of risks, benefits and consequences of treatments." We do not feel like the guideline supports this commitment as it stands. Final decisions on when and how to treat should be a collaborative decision between a multidisciplinary heart team and the patient, and be based on the most up to date evidence. As per the NICE guideline on 'Patient experience in adult NHS services: enabling patients to actively participate in their care', which states that clinicians should "Offer support to the patient when they are considering options", and "use the principles of shared decision making." Furthermore, the GIRFT Programme National Specialty Report (2021) states that "Multidisciplinary meetings (MDMs) are an essential part of cardiology treatment pathways and a core function of the heart team", and we believe the role of MDT's on decision on when and how to treat should be stressed in the guideline. The report continues to say that "Currently, there is significant variation in access to regular, quorate cardiovascular MDMs. The main reasons for this are lack of access to appropriate technology and lack of availability of multidisciplinary team (MDT) members. MDMs should be virtual by default. Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed." We believe clear guidance in the guidelines on makeup of MDT, the role of the heart team and Care plans will improve patient experience and patient outcomes.	MDTs as an example of how this may be provided. We support shared decision making in the guideline (see recommendations (see 1.5.1) however we are only able to recommend choice when between interventions which are shown to be cost effective.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We support the GIRFT Programmes National Speciality Report's assertion that "Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed. A clinician who is familiar with the patient and their needs and preferences should present their case." This construction of and MDT will put patients at the centre of their care, ensure they have access to all clinically appropriate treatment options, and support their views that treatment decisions should be based on 'Heart Team', 'Patient Choice' and 'Up to date evidence' - in line with NICE's Guideline on Patient Experience. **References** **1.** Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021 **2.** NICE Guideline, Patient experience in adult NHS services: enabling patients to actively participate in their care, 2012, **https://pathways.nice.org.uk/pathways/patient-experience-in-adult-nhs-services/patient-experience-in-adult-nhs-services-enabling-patients-to-actively-participate-in-their-care#content=view-info-category%3Aview-about-menu,** Accessed April 2021. Dr Sarah Clarke and Professor Simon Ray, GIRFT Programme National Specialty Report (2021), https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf, Accessed April 2021.	
Heart Valve Voice	Guideline	011	016 - 019	Heart Valve Voice celebrate the guidelines commitment to patient preference when determining when to treat. Through consultation, we have found that patients are prepared to travel for treatment when clinically	Thank you for comment. The committee anticipate that the current recommendation will ensure that

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				appropriate. Furthermore 94% of patients surveyed felt frustration at treatment options denied based on limited availability or local restrictions. However, we have also found evidence that although referrals to another centre for minimally invasive surgery is current practice, it is not always followed. We believe the guideline needs to go further, by explaining all clinically appropriate treatment options to the patient in consultation, and provide the patient with a list of centres where these therapies are available. Our webinar found that 37.9% patients were not made aware of therapies that were clinically appropriate for them, with a further 45% of patients surveyed reporting that it was not explained to them why they were or were not suitable for minimal invasive or transcatheter procedures. The guideline needs strengthening to ensure all patients are given a range of clinically appropriate opportunities to treat. **References** 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	minimally invasive treatment is offered where appropriate. NICE guidelines are unable to recommend that a list of centres is provided but this may form part of the discussion with the patient when discussing the treatment options.
Heart Valve Voice	Guideline	012	003 - 012	We are concerned that language of 'first-line intervention 'will limit patient choice. Evidence suggests that where clinically appropriate, percurtaneosus interventions lead to better outcomes and better patient experience. Through our consultation, we found that 94% patients were frustrated by treatment options limited due to geographical inequalities and lack of local clinical expertise. While we do not feel like we should be involved in cost-modelling, we do feel we should reference Malcolms Story. The recommendations in the report can help to remedy the problem of	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				treatment access by delivering optimal treatment of heart valve disease, rather than increasing the burden on the NHS. These solutions can actually help to save costs in the longer term, by keeping patients out of hospital and living independent lives. The Nice Guidance on 'Patient experience in adult NHS services: enabling patients to actively participate in their care' states that clinicians should "ensure that the patient is aware of the options available and explain the risks, benefits and consequences of these", and "encourage the patient to clarify what is important to them, and check that their choice is consistent with this." We do not believe the guideline as it stands supports this commitment to patient choice. We are concerned that the language of 'is unsuitable 'in regards to TAVI will lead to worse patient experience and deepen pre-existing regional variation in treatment. **References** 1. Unwarranted Variation Scenario: The variation between suboptimal and optimal pathways, (2018), <https://heartvalvevoice.com/application/files/4115/7891/9799/Unwarranted_Variation_Scenario.pdf> Accessed April 2021. NICE Guideline, Patient experience in adult NHS services: enabling patients to actively participate in their care, 2012, **https://pathways.nice.org.uk/pathways/patient-experience-in-adult-nhs-services/patient-experience-in-adult-nhs-services-enabling-**	We have added a cross reference to the NICE guideline on shared decision making to recommendation 1.5.1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patients-to-actively-participate-in-their-care#content=view-info-category%3Aview-about-menu, Accessed April 2021.	
Heart Valve Voice	Guideline	014	008 - 015	We support the recommendation that decisions on intervention should be a shared decision. However, we are concerned that patients individual circumstance are not explicitly stated as part of the shared decision making process. Consultation with patients told us that lifestyle (work, caring responsibilities, social life) was an important contributing factor when making decisions on what treatment to have. **References** 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	Thank you for your comment. We have added the importance of lifestyle factors to the committee's discussion of the evidence in evidence review I.
Heart Valve Voice	Guideline	016	002 - 021	We support the recommendation on information and advice to patients. However, through consolation we found that only 4% of a webinar group and 8% of responders to an online survey were offered information on mental health, therefore we recommended the language 'consider 'be changed to 'offer 'to ensure all patients have access to necessary information and advice. Furthermore we are concerned that the language here doesn't stress the importance of providing the patient with up to date, clear, and suitable information. From consultation, the quality of the information received by patients was average to poor in regards to Wound Care, Valve Care, Mental Health Support and Aftercare. The guidelines must do more to stress the importance of up to date, quality, holistic information given to all heart valve disease patients at all points in their pathway.	Thank you for your comment. Due to the potential resource impact of the provisions of psychological support and in the absence of evidence the committee were could not make an 'offer' recommendation. Recommendation 1.9.1 signposts to the NICE guideline on patient experience of adults NHS services. This guideline contains recommendations on patient information to promote their active participation in care and self-management. We have added your

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				References 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	examples to the committee discussion of the evidence in evidence review L.
Heart Valve Voice	Guideline	019	010 - 011	We support the need for further research into information and advice needs for all adult age groups with heart valve disease of all severities. From consultation we found that patients saw huge variation in quality of information they received, and saw a need for patient-led information. Heart Valve Voice will work with patients, key stakeholders and NHS providers to develop patient resources that are truly independent and patient led.	Thank you for your comment.
Heart Valve Voice	Guideline	023	011 - 016	Evidence suggests that the confidence with which GP's can listen to hearts and detect the severity of a murmur is at 48%. Coupled with our online survey finding 26% of patients who reported to their GP with symptoms and a further 43% our webinar attendees, did not have their heart listened to. This suggests a lack of awareness of heart valve disease in primary care. We are concerned that a stethoscope check alone could lead to patients of a variety of ages being diagnosed later and leading to worse outcomes. Heart Valve Voice 'Primary Care Guidance states that "Echocardiography is indicated in any patient with a heart murmur if there is any suspicion of valve disease on clinical examination." A 2020 Heart Health Survey of over 60s found awareness of heart valve disease remains, with only 5.6% of people able to correctly describe what aortic stenosis was. The survey found that "Neither appointments with a GP driven by symptoms nor regular use of a stethoscope are a reliable guarantee for early diagnosis.",	Thank you for your comment. We expect that the recommendations on referral for echocardiography and specialist assessment will improve the diagnosis of people with heart valve disease. Recommendations 1.1.1 recommends that all people with a murmur should be referred if heart valve disease is suspected.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				therefore timely referral to echocardiography should be prioritised for all patients who present with a murmur. Furthermore, the NHS Long Term Plan states that "Early detection and treatment of CVD can help patients live longer, healthier lives" and by leaving missed opportunities to detect and diagnose early, the guideline will not help progress the NHS Long Term Plan. **References** 1. Birrane, J.P., Lim, Z.L., Liew, C.H. *et al.* A survey of general practitioners' knowledge and clinical practice in relation to valvular heart disease. *Ir J Med Sci* (2021). https://doi.org/10.1007/s11845-021-02619-x 2. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021 3. Heart Valve Voice, Primary Care Guidance (2018), https://heartvalvevoice.com/application/files/8415/8436/2829/104_-_Practical_Guidance_FINAL.pdf, Accessed March 2021. 1. Gaede, L, Sitges, M, Neil, J, et al. European heart health survey 2019. *Clin Cardiol*. 2020; 43: 1539– 1546. https://doi.org/10.1002/clc.23478 NHS Long Term Plan (2019(, Page 62, https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf, Accessed March 2021.	
Heart Valve Voice	Guideline	023	001 - 005	Evidence suggests that the confidence with which GP's can listen to hearts and detect the severity of a murmur is at 48%. Coupled with our online survey finding 26% of patients who reported to their GP with symptoms and 43% our webinar attendees not having their heart listened to, there seems	Thank you for your comment. We expect that the recommendations on referral for echocardiography and specialist assessment will improve the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to be a lack of awareness of heart valve disease in primary care. We are concerned that a stethoscope check alone could lead to patients of a variety of ages being diagnosed later and leading to worse outcomes. Heart Valve Voice 'Primary Care Guidance states that "Echocardiography is indicated in any patient with a heart murmur if there is any suspicion of valve disease on clinical examination." A 2020 Heart Health Survey of over 60s found awareness of heart valve disease remains, with only 5.6% of people able to correctly describe what aortic stenosis was. The survey found that "Neither appointments with a GP driven by symptoms nor regular use of a stethoscope are a reliable guarantee for early diagnosis.", therefore timely referral to echocardiography should be prioritised for all patients who present with a murmur. Furthermore, the NHS Long Term Plan states that "Early detection and treatment of CVD can help patients live longer, healthier lives" and by leaving missed opportunities to detect and diagnose early, the guideline will not help progress the NHS Long Term Plan. **References** 1. Birrane, J.P., Lim, Z.L., Liew, C.H. *et al.* A survey of general practitioners' knowledge and clinical practice in relation to valvular heart disease. *Ir J Med Sci* (2021). https://doi.org/10.1007/s11845-021-02619-x 2. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	diagnosis of people with heart valve disease. Recommendation 1.1.1 recommends that all people with a murmur should be referred if heart valve disease is suspected.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				3. Heart Valve Voice, Primary Care Guidance (2018), https://heartvalvevoice.com/application/files/8415/8436/2829/104_-_Practical_Guidance_FINAL.pdf, Accessed March 2021. 1. Gaede, L, Sitges, M, Neil, J, et al. European heart health survey 2019. *Clin Cardiol*. 2020; 43: 1539– 1546. https://doi.org/10.1002/clc.23478 NHS Long Term Plan (2019(, Page 62, https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf, Accessed March 2021.	
Heart Valve Voice	Guideline	023	026	We are concerned that maintaining current practice in detection of heart valve disease will lead to missed opportunities, later diagnosis and worse outcomes for patients. Evidence suggests that the confidence with which GP's can listen to hearts and detect the severity of a murmur is at 48%. With the prevalence of heart valve disease increasing, GP's need to be listening to more hearts and referring swiftly to echocardiography to ensure we can detect and treat patients earlier. Heart Valve Voice 'Primary Care Guidance states that "Echocardiography is indicated in any patient with a heart murmur if there is any suspicion of valve disease on clinical examination." A 2020 Heart Health Survey of over 60s found awareness of heart valve disease remains, with only 5.6% of people able to correctly describe what aortic stenosis was. The survey found that "Neither appointments with a GP driven by symptoms nor regular use of a stethoscope are a reliable guarantee for early diagnosis.", therefore timely referral to echocardiography should be prioritised for all patients who present with a murmur.	Thank you for your comment. We expect that the recommendations on referral for echocardiography and specialist assessment will improve the diagnosis of people with heart valve disease. Recommendation 1.1.1 recommends that all people with a murmur should be referred if heart valve disease is suspected.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Furthermore, the NHS Long Term Plan commits to 'early detection and treatment of CVD' and we believe the current guideline does not match the increasing prevalence of the disease, the detection and diagnostic backlog caused by Covid or the commitment in the NHS Long Term Plan to earlier detection and treatment. Our consultation found that 26% of patients surveyed and 43% of patients interviewed who presented with symptoms did not have their heart listened to when first presenting with symptoms, suggesting a lack of awareness of the red flag symptoms of heart valve disease at primary care level. Better education or adoption of new technologies that improve the accuracy with which clinicians can listen to hearts is required if current practice is to be continued. If not, we will continue to see missed opportunities and later detection of heart valve disease. **References** 1. Birrane, J.P., Lim, Z.L., Liew, C.H. *et al.* A survey of general practitioners' knowledge and clinical practice in relation to valvular heart disease. *Ir J Med Sci* (2021). https://doi.org/10.1007/s11845-021-02619-x 2. Heart Valve Voice, Primary Care Guidance (2018), https://heartvalvevoice.com/application/files/8415/8436/2829/104_-_Practical_Guidance_FINAL.pdf, Accessed March 2021. 1. Gaede, L, Sitges, M, Neil, J, et al. European heart health survey 2019. *Clin Cardiol*. 2020; 43: 1539– 1546. https://doi.org/10.1002/clc.23478 3. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				NHS Long Term Plan (2019(, Page 62, https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf, Accessed March 2021.	
Heart Valve Voice	Guideline	024	006 - 008	We support the view that mild and moderate valve disease does not necessitate the need for 'urgent' specialist assessment in most cases, but these patients do require echos to assess the severity of their disease with accuracy. 1. Heart Valve Voice, Primary Care Guidance (2018), https://heartvalvevoice.com/application/files/8415/8436/2829/104_-_Practical_Guidance_FINAL.pdf, Accessed March 2021.	Thank you for your comment. The committee have made a new recommendation for monitoring in mild aortic and mitral stenosis (1.4.2). Due to the variation in current clinical practice, they were unable to make a recommendation for moderate disease but have made a research recommendation.
Heart Valve Voice	Guideline	024	016 - 017	Urgent referral for specialist assessment or urgent echocardiography should happen in 2 weeks as per Heart Valve Voice's clinically approved Gold Standard of Care. Through consultation, we found 26% of patients were not told why they were waiting for an echo, which left them feeling 'anxious 'and 'scared.' **References** 1. Heart Valve Voice, A Gold Standard in the Diagnosis,Treatment and Management of Heart Valve Disease in Adults (2019) Page 12. https://heartvalvevoice.com/application/files/9315/8436/2679/Gold_Standard__of_Care_For_Print.pdf Accessed April 2021 Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	Thank you for your comment. This has been edited to 2 weeks.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Heart Valve Voice	Guideline	024	023	We are concerned that maintaining current practice in detection of heart valve disease will lead to missed opportunities, later diagnosis and worse outcomes for patients. Evidence suggests that the confidence with which GP's can listen to hearts and detect the severity of a murmur is at 48%. Evidence recently given to the All-Party Parliamentary Group for Heart Valve Disease found that the prevalence of heart valve disease is increasing, however current detection and treatment levels are not in line with the prevalence of the disease, GP's need to be listening to more hearts and referring swiftly to echocardiography to ensure we can detect and treat patients earlier. **References** 1. Birrane, J.P., Lim, Z.L., Liew, C.H. *et al.* A survey of general practitioners' knowledge and clinical practice in relation to valvular heart disease. *Ir J Med Sci* (2021). https://doi.org/10.1007/s11845-021-02619-x Heart Valve Voice, All-Party Parliamentary Group for Heart Valve Disease Evidence Sessions (2021) https://heartvalvevoice.com/Advocacy/APPG	Thank you for your comment. We expect that the recommendations on referral for echocardiography and specialist assessment will improve the diagnosis of people with heart valve disease. In the experience and opinion of the committee most GPs and non-cardiology physicians would be able to distinguish between murmurs but they should refer if there is a suspicion of heart valve disease (recommendation 1.1.1).
Heart Valve Voice	Guideline	030	004	Through our consultation, we found that 50% of patients were unable to easily recognise and explain their own symptoms to their clinician, with a 43% of those patients not receiving a stethoscope check. Stress Testing would help to expose symptoms which patients are either masking or unable to recognise in themselves. 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	Thank you for your comment. The committee were able to make recommendations on stress echocardiography for aortic stenosis (1.3.2) and mitral regurgitation (1.3.8). In addition, in recognition of the importance of this topic the committee made research recommendations (see appendix K in evidence review E).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Heart Valve Voice	Guideline	034	012	We support the recommendation that timing of monitoring for patients with severe aortic stenosis should be decided through shared decision making with the patient. However, through consultation, we found that patients with all levels of severity of valve disease found monitoring to be important to their patient experience, making them feel more 'looked after 'and 'relieved. 'Our patients say, once they hear a murmur, they get limited information (70% received nothing), and don't feel part of their pathway, with lack of regular monitoring leaving them 'anxious', 'scared 'and 'worried. 'However, those that did receive local, regular surveillance felt 'reassured 'and 'pleased to be under a cardiologists care.' It is our view that the guidelines should recommend offering monitoring for patients with all severities of heart valve disease, with the regularity determined through shared decision making by patient and clinician. **References** Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021.	Thank you for your comment. The committee has made a new recommendation for monitoring in mild aortic or mitral stenosis (1.4.2). Due to the current variation in clinical practice the committee were unable to make a consensus recommendation on moderate disease. The committee made a research recommendation on frequency of monitoring (see appendix J in evidence review G).
Heart Valve Voice	Guideline	035	007 - 010	We support the committee's view on the importance of shared decision making. When asked, patients said that 'patient choice 'and 'shared consultation 'were priorities for them when taking part in our NICE Guideline consultation. **References**	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021.	
Heart Valve Voice	Guideline	035	015 - 017	Heart Valve Voice support the committees view that 'decision to treat should be based on patient characteristics and preferences', but with it only making a small change to current practice, we believe the language needs to be stronger to ensure all patients are offered access to all clinically appropriate therapies. 46% of patients consulted were not told why they were or were not suitable for transcatheter or minimal invasive procedure. Language in the guidelines needs to be stronger to ensure all patients have access to all therapies. It is our recommendation that the guidelines give access for patients to a strong MDT which discuss all treatment options to ensure patients are directed to the option which will provide the best outcome for them, their symptoms and their long term health. The influence of multidisciplinary heart teams and up to date evidence was found to be the most important to patients when deciding on treatment. We believe the guidelines need to be clearer in regards to role of the MDT's and Care Plans like the 'NICE Guideline for Chronic heart failure in adults: diagnosis and management 2018', which clearly maps the make up and role of MDT's and the importance of clear Care Plans. In its current format, the guidance will put limits on patient choice and shared decision making, as mapped out in NICE's guideline for 'Patient experience in adult NHS services: enabling patients to actively participate in their care.' Furthermore, the GIRFT Programme National Specialty Report (2021) states that "Multidisciplinary meetings (MDMs) are an essential part of	Thank you for your comment. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cardiology treatment pathways and a core function of the heart team. Currently, there is significant variation in access to regular, quorate cardiovascular MDMs. The main reasons for this are lack of access to appropriate technology and lack of availability of multidisciplinary team (MDT) members. MDMs should be virtual by default. Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed." We support the GIRFT Programmes National Speciality Report's assertion that "Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed. A clinician who is familiar with the patient and their needs and preferences should present their case." This construction of and MDT will put patients at the centre of their care, ensure they have access to all clinically appropriate treatment options, and support their views that treatment decisions should be based on 'Heart Team', 'Patient Choice' and 'Up to date evidence' - in line with NICE's Guideline on Patient Experience. **References** 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021. 2. NICE Guideline for Chronic heart failure in adults: diagnosis and management 2018. <https://www.nice.org.uk/guidance/ng106/chapter/Recommendations#monitoring-treatment-for-all-types-of-heart-failure> Accessed April 2021	importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				3. NICE Guideline, Patient experience in adult NHS services: enabling patients to actively participate in their care, 2012, **https://pathways.nice.org.uk/pathways/patient-experience-in-adult-nhs-services/patient-experience-in-adult-nhs-services-enabling-patients-to-actively-participate-in-their-care#content=view-info-category%3Aview-about-menu,** Accessed April 2021. Dr Sarah Clarke and Professor Simon Ray, GIRFT Programme National Specialty Report (2021), https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf, Accessed April 2021.	
Heart Valve Voice	Guideline	038	017 - 019	Through our consultation we found that patients wanted decisions on which clinically appropriate treatment to receive to be determined by themselves, (25%) and their Heart Team (29%) , with 27% prioritising treatment based on the most up to date evidence. Most patients when asked, stressed the need for patient choice to be a the centre of these guidelines. Furthermore, 40% of patients consulted were not informed of all treatment options clinically available to them, and we believe without clear guidance on MDT's and Care Plans (see NICE Guideline for Chronic heart failure in adults: diagnosis and management 2018) the guidance will put limits on patient choice, shared decision making (as set out in NICE Guidelines on Patient Experience) and access to treatments which result in better outcomes both in terms of symptoms and long term health.' Furthermore, the GIRFT Programme National Specialty Report (2021) states that "Multidisciplinary meetings (MDMs) are an essential part of cardiology treatment pathways and a core function of the heart team. Currently, there is significant variation in access to regular, quorate	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee agree on the importance of shared-decision making and this is highlighted in recommendations 1.5.1 and 1.9.1

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cardiovascular MDMs. The main reasons for this are lack of access to appropriate technology and lack of availability of multidisciplinary team (MDT) members. MDMs should be virtual by default. Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed." We support the GIRFT Programmes National Speciality Report's assertion that "Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed. A clinician who is familiar with the patient and their needs and preferences should present their case." This construction of and MDT will put patients at the centre of their care, ensure they have access to all clinically appropriate treatment options, and support their views that treatment decisions should be based on 'Heart Team', 'Patient Choice' and 'Up to date evidence' - in line with NICE's Guideline on Patient Experience. **References** 1. Heart Valve Voice NICE Patient Consultation (2021), <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021. 2. NICE Guideline for Chronic heart failure in adults: diagnosis and management 2018. <https://www.nice.org.uk/guidance/ng106/chapter/Recommendations#monitoring-treatment-for-all-types-of-heart-failure> Accessed April 2021 Dr Sarah Clarke and Professor Simon Ray, GIRFT Programme National Specialty Report (2021), https://www.gettingitrightfirsttime.co.uk/wp-	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf, Accessed April 2021.	
Heart Valve Voice	Guideline	048	013 - 023	Heart Valve Voice support the committees recommendation for a single point of contact for heart valve disease patients, and have recently began to create a network of Heart Valve Disease Patient Champions, who could act as a support network for future valve disease patients. We also support the commitment to improved information for all valve disease patients. Through our consolation with over 100 patients, we found huge variation in both the range and quality of information provided to patients. Despite this, there was real appetite from patients to help drive better, standardised, patient-led information. We support the commitment to individualised care and shared decision making, and found 'collaborative decision making 'to be one of the most important factors patients wanted included in the NICE Guidelines for Heart Valve Disease. **References** Heart Valve Voice NICE Patient Consultation 2020, <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	Thank you for your comment
Heart Valve Voice	Guideline	General	General	Heart Valve Voice recommends that the guideline include clearer guidance on team working in management of heart valve disease and a clear care plan for patients, as is recommended in NICE Guideline for Chronic heart failure in adults: diagnosis and management 2018.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				From consultation, we found that patients wanted decisions on treatment to be based on the Heart Team 29.5%, the most up to date evidence 27.2% and patient choice, 25.9. Furthermore, patients found monitoring before treatment made them feel 'reassured' and 'looked after.' A clear and detailed care plan for management of their condition and a strong Multidisciplinary Team would likely lead to patients feeling more confident and assured in their treatment pathway, and lead to better patient experience. We support the view that "The Heart Team should provide a consensus view as to which treatment strategy is superior based on the available evidence as well as the collective experience of individual specialists and their unit generally', and believe the guideline should include specific guidance on MDT's and Care Plans which include all clinically appropriate treatments available for the patient. Furthermore, the GIRFT Programme National Specialty Report (2021) states that "Multidisciplinary meetings (MDMs) are an essential part of cardiology treatment pathways and a core function of the heart team. Currently, there is significant variation in access to regular, quorate cardiovascular MDMs. The main reasons for this are lack of access to appropriate technology and lack of availability of multidisciplinary team (MDT) members. MDMs should be virtual by default. Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed."	importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee agree that monitoring is important see recommendations 1.4.1 and 1.8.1.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We support the GIRFT Programmes National Speciality Report's assertion that "Core members should be job planned to attend, and there should be scope for bringing in additional clinical opinion as needed. A clinician who is familiar with the patient and their needs and preferences should present their case." This construction of and MDT will put patients at the centre of their care, ensure they have access to all clinically appropriate treatment options, and support their views that treatment decisions should be based on 'Heart Team', 'Patient Choice' and 'Up to date evidence' - in line with NICE's Guideline on Patient Experience. **References** 1. NICE Guideline for Chronic heart failure in adults: diagnosis and management 2018. <https://www.nice.org.uk/guidance/ng106/chapter/Recommendations#monitoring-treatment-for-all-types-of-heart-failure> Accessed April 2021 2. Heart Valve Voice NICE Patient Consultation 2020, <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021 3. European Journal of Cardio-Thoracic Surgery, Volume 48, Issue 4, October 2015, Pages 524–529, https://doi.org/10.1093/ejcts/ezv083, Accessed April 2021. **https://academic.oup.com/ejcts/article/48/4/524/2464969** Dr Sarah Clarke and Professor Simon Ray, GIRFT Programme National Specialty Report (2021), https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf, Accessed April 2021.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Heart Valve Voice	Guideline	General	General	Heart Valve Voice support many of the recommendations in this guideline, In particular the stress on shared decision making and patient choice creates a guideline that is built on collaborative decision making between patient and clinician that will likely improve patient experience. With stronger guidance on MDT's and Care Plans, the guidelines will make patients a central part in their pathway. However, we do believe the guideline is conservative in places, and rather than challenge commissioners and policymakers to do more to improve the structures that improve the diagnosis, detection and treatment of heart valve disease, the guideline sets itself within the limitations of the NHS where workforce and lack of access to diagnosis and treatment means treatment levels for heart valve disease remain low. In regards to echocardiography, patients explicitly stated that regular echos made them feel more 'confident' and 'relieved', yet the guidelines put limitations on access to echo based on workforce pressures. A 2016 study found that between 800-1000 new echocardiographers will need to be trained over the next 4-5 years to meet demands on echo. With the pressure on echo likely to increase due to diagnostic backlogs caused by Covid, these guidelines are an opportunity to challenge policymakers to fulfil the workforce gap and retain that workforce when those pressures subside. This increased workforce will allow us to referr more patients and earlier, and lead to better outcomes and patient experience. **References**	Thank you for your comment. The guideline recommends the most clinical and cost effective tests and interventions based on the current evidence base and we anticipate that these will improve patient care. Service delivery was outside of the scope of this guideline but we expected that some services will change in order to implement the recommendations. Only limited evidence was reported on referral to echocardiography. Due to the potential resource impact we were unable to make recommendations for more regular echocardiography.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. Oakley. P. Improving Cardiac Care: Developing the Echo Service CSO's Policy Programme: Managing Service Demand and Transforming the Service Delivery Model Modelling the Future Workforce in Cardiac Physiology, (2016), http://www.bcs.com/documents/SRCPS_Final_report_12052015_2.pdf, Accessed April 2020. Heart Valve Voice NICE Patient Consultation 2020, <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021	
Heart Valve Voice	Guideline	General	General	Throughout our Patient Consultation, we engaged 100 patients with an online survey and 59 in a interactive webinar. Ages in the group ranged from 36-87, and participants were from a range of backgrounds and ethnicities. In doing so, we sought to understand their experience of heart valve disease treatment and how they believe it can be improved. This kind of meaningful patient engagement has allowed us to create a response that is truly patient-led. It is our belief that multi-industry funded Patient Organisations, such as Heart Valve Voice, would be invaluable members of committees that determine NICE Guidelines, and empower NICE to put patients' lived experiences at the heart of new guidelines. In addition to this, the GIRFT Programme National Specialty Report (2021) states that "Any service redesign must have patient-centred care at its heart" and we believe utilising the strong patient voice Patient Organisations have will help to ensure that guidelines and frameworks are patient led.	Thank you for your comment. We encourage people to apply as a lay member on NICE guidelines. Further information on the Patient and public involvement team at NICE can be found here https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/public-involvement-programme. There were two lay members on the committee for this guideline. We thank you for your responses and value the fact that they are patient-led.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				References 1. Heart Valve Voice NICE Patient Consultation 2020, <https://heartvalvevoice.com/Advocacy/advocate/nice-guidelines-patient-consultation-group> Accessed April 2021 Dr Sarah Clarke and Professor Simon Ray, GIRFT Programme National Specialty Report (2021), https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf, Accessed April 2021.	
Hull University Teaching Hospitals NHS Trust	Guideline	009	001	We are concerned that this statement will discourage aortic valve intervention with TAVI. Taking into account calcium distribution is essential for both SAVR and TAVI as both have anatomical considerations. However, in most circumstances, this is not prohibitive to TAVI and there are valve options to tailor towards the patient's anatomy. We feel that this is misleading, as patients with high calcium burden indicates severe aortic stenosis and hence should be considered for TAVI if appropriate. We feel that this is an unnecessary statement and discourages TAVI if appropriate patients	Thank you for your comment. This recommendation was based on the available evidence showing poor outcomes after TAVI in people with very high calcium score. Although high calcium burden indicates severe aortic stenosis extremely high calcium burden, asymmetric distribution and calcium burden in the left ventricular outflow tract increase the risk of the TAVI procedure and the likelihood of unwanted consequences like paravalvular leak. The recommendation does not advise against TAVI in these patients, but highlights calcium burden and distribution as a factor to consider. If

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					surgery is more appropriate this is still an option.
Hull University Teaching Hospitals NHS Trust	Guideline	012	004	Surgery should not routinely be first line in all patients. The evidence does not support this	Thank you for your comment. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Hull University Teachin	Guideline	012	006	Non-bicuspid valve disease should not be lumped together as bicuspid valve valve can be treated with TAVI in appropriate patients	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
g Hospitals NHS Trust					covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.
Hull University Teaching Hospitals NHS Trust	Guideline	012	007	The evidence does not support TAVI only if patients are unsuitable for surgery	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					evidence meeting the review protocol criteria (see Appendix A).
Hull University Teaching Hospitals NHS Trust	Guideline	036	019	We disagree with this statement. This is not in keeping with daily practice and does not adequately distinguish high, medium or low risk patients.	Thank you for your comment. The model has been revised to account for contemporary practice and current outcomes and risk groups are now distinguished for mortality (early and long-term), costs and quality of life. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Hull University	Guideline	038	017	We disagree with this statement. We are concerned that this will place greater emphasis on surgeons to take on high risk cases unnecessarily. This could push surgeons outside their comfort zone. If a local surgical	Thank you for your comment. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Teaching Hospitals NHS Trust				department does not take on a high risk SAVR, this would leave the patient with no treatment option as TAVI would be deemed 'unsuitable' as the patient would have been a surgical candidate, albeit high risk. This would exclude a significant proportion of patients and result in greater harm. In addition, this in turn will lead to the development of surgical centres with 'high risk' expertise and deny timely access to treatment. This would be regressive step in dealing with the aortic stenosis challenge nationally.	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Hull University Teaching Hospitals NHS Trust	Guideline	038	018	Overall, we feel that this document does not reflect current evidence and best practice. Above all, this document is not patient centred or patient focussed. We feel that this is biased towards SAVR and minimally invasive surgery. If implemented this will have serious implications and deny suitable patients timely and appropriate treatment, and would be a regressive step in the treatment of aortic stenosis. Both cardiologists and cardiac surgeons should work collaboratively in treating aortic stenosis. This document unfortunately does not aid in that integration process, and further amplifies the 'us and them' attitude.	Thank you for your comment. All evidence meeting the review protocol criteria was included in the guideline. Quality of life was included as an outcome in the protocol for the interventions review (Appendix A evidence review H). In addition, there were two lay members on the committee who contributed their experience and this was considered when formulating the recommendations.
Imperial College Healthc		013 006	Table 2 16	1) Data from CtE shouldn't be used in the assessment of Mitraclip as this included the learning curves of all 3 centres and outcomes were demonstrably less good than other published randomised studies and	Thank you for your comment. 1) CtE was not used to calculate treatment effects, as this is not a

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
are NHS Trust		Mitral valve disease-regurgitation		registries. The document makes a similar criticism of Mitra-FR but doesn't apply the same criteria to CtE. 2) We would question the assertion that Mitraclip has been commissioned by NHS England . For a service to be commissioned one would need to have had a competitive tendering process. This has never been undertaken.	randomized controlled trial but an observational study. It was used, instead, for other parameters that are not supposed to be affected by learning curves, such as the cost of the procedure and some of the characteristics of the patients. 2) NHS England has produced a clinical commissioning policy for Percutaneous mitral valve leaflet repair for primary degenerative mitral regurgitation. This has now been made clear in the report.
Imperial College Healthcare NHS Trust		Minimal access surgery		The recommendations suggest patients should be given the choice of minimal-access surgery, even referring to other centres if expertise is not available locally. There is no evidence to say median sternotomy is superior or inferior to minimal access surgery except for the cosmetic effect. It is odd that in this regard, patient choice is seen as paramount, but in choosing TAVI or AVR, it is not.	Thank you for your comment. The committee agreed that in their clinical experience there was no difference between minimally invasive and standard surgery replacement in terms of clinical outcomes when performed by those with expertise in minimally invasive surgery. The resource impact of these recommendations is minimal. In contrast, TAVI was found to be cost effective for high risk patients only. There is a considerable resource impact of recommending TAVI for low

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					and intermediate risk patients. It was therefore not possible to recommend a choice between surgery and TAVI for these patients. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust		Mitral valve disease-stenosis		We agree with the recommend Balloon mitral valvuloplasty (BMV) if anatomically suitable in mitral stenosis, and Imperial offers this. We agree that MVR be offered if BMV is not possible.	Thank you for your comment.
Imperial College Healthcare NHS Trust		Mitral valve disease-regurgitation		We agree with the recommendation for mitral valve repair for primary mitral regurgitation, preferably with minimal access surgery. We disagree that a patient would be referred out if minimal access surgery is not available. This will increase waiting lists and travel times. We agree that MVR be offered if repair is not suitable.	Thank you for your comment. The options would be discussed with the person in the context of shared decision making and this would include any impact on travel and waiting times if minimally invasive surgery is not available locally. We cross refer to the NICE guideline on shared decision making in recommendation 1.5.1
Imperial College Healthc		Redo valve interv		If we read the guidance correctly, redo-surgery is seen as 1st line therapy. We disagree, and feel that the MDT should choose which therapy- redo	Thank you for your comment. Both transcatheter or redo surgical intervention are included as options in

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
are NHS Trust		entions		surgery (if a mechanical valve) or catheter based valve –in-valve therapy (if a bioprosthetic valve) is best.	recommendations 1.6.1. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Imperial College Healthcare NHS Trust		Tricuspid Valve intervention		We agree research is needed, and Imperial is about to start a tricuspid valve intervention program in 2021. We feel that NHS England should provide funding to allow the program to be initiated.	Thank you for your comment. We have made a research recommendation on the most clinical and cost effective management strategy for tricuspid regurgitation (see appendix J evidence review H) which we hope will support trials in this area.
Imperial College Healthcare NHS Trust		Valve assessment		We would consider it best practice to mandate: -Echo valve clinics (physiology led) (located in 'diagnostics hubs'- as per the NHS 10 yr plan) , as first line assessment for murmur patients so they are diagnosed and fed into the correct treatment pathway as will be directly overseen by echo valve specialists.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				-Specialist valve clinics to facilitate timely and appropriate medical and interventional treatment (as per BHVS guidance)- We have cardiac surgery, cardiology and care of the elderly clinic in one setting to avoid patient journeys and reduce delays	
Imperial College Healthcare NHS Trust	Economic report TAVI	014	Table	Procedural costs for TAVI ae based incorrectly on on NHS Reference costs, £9658 for intermediate-risk and £11979 for high-risk. Analysis from Liverpool Heart & Chest Hospital of PLICS data for 244 TAVIs in a recent calendar year showed the average cost of TAVI to be £6332. For trans-femoral TAVI it was £5678. Analysis of PLICS data from Leeds Teaching Hospitals NHS Trust found an average TAVI cost of £5322 per patient. The base case should be revised to reflect the lower true cost of TAVI, or at the very least the different potential cost of the TAVI procedure should be added to the sensitivity analyses.	Thank you for your comment and for sharing your information. We revised our methodology to calculate the cost of a TAVI procedure, using a UK source to extrapolate LOS and ICU – the UK TAVI trial. The costs of (transfemoral) TAVI used in the model is now: Low-risk: £5,479 Intermediate-risk: £5,540 High-risk: £5,575 This seems to be in line with the cost of trans-femoral TAVI reported by your institution, which confirms that the model is now capturing the real cost of a TAVI procedure. We have revised the economic model based on stakeholder comments and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust	Economic report TAVI	016	Table	The data used on costs of ICU stay for TAVI are inappropriate- ICU is usually NOT needed for TAVI. The Model has based costs on an average ICU stay of 2 days for intermediate risk patients, and 3 days for high-risk. These assumptions are based on data from the trials which are old reflect the US model of care for TAVI. Currently in the NHS patients do not go to ICU at all after TAVI. The average number of days on ICU for TAVI in the NHS is Zero for intermediate risk and Zero for high-risk. These data are evident from the UK TAVI trial, in which the median length of stay on ICU was 0 days for TAVI (inter-quartile range 0,0), versus median 1 day (IQR 1,3) for surgery. This has led to a major overestimation of the costs of the TAVI procedure.	Thank you for your comment. After further discussion, the committee agreed to use UK data for length of hospital stay and ICU stay as it appears clear that the practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust	Economic report TAVI	017	Table	The data used for Total Length of Stay are also inappropriate. The model uses a LOS of 6 and 8 days for TAVI in intermediate and high risk respectively vs 9 and 11 days for surgery. This is very far from current practice for TAVI. Hospital stay was much lower in PARTNER 3 and Evolut Low Risk. The UK TAVI trial data show median LOS 3 days for TAVI vs 8 days for SAVR. UK TAVI registry data show median LOS 2 days for TAVI. This has further contributed to overestimation of the costs of the TAVI procedure. Imperial data is a median LOS of 3 days in the last 500 TAVI.	Thank you for your comment. After further discussion, the committee agreed to use UK data for Length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthc	Economic	General		The economic model is flawed with inappropriate cost data. Although the valve is expensive compared to surgical valves, the cost saving with reduced LOS and no ITU stay should be balanced. The analysis will be	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
are NHS Trust	report TAVI			sensitive to the actual costs allocated and the time estimated in ITU, HDU and hospital ward. A reasonable comparison would be on 10 year time horizon, and Tissue Surgical valve versus TAVI. The model uses 30 years. In addition, all TAVI patients should be included. The younger patients, who will live longer, would have more impact in any analysis. Comparing only older patients, who will have a shorter life expectancy, will disadvantage TAVI in current UK practice.	All the savings due to reduced length of hospital stay and ICU stay were included in the model. Moreover, the model accounts for saving occurring downstream associated with the rehabilitation of the patients at home or at an intermediate care centre. UK TAVI trial data are used for length of hospital stay and ICU stay days to better reflect the current practice in the UK in the revised version of the model. The committee agreed to assume a time-horizon of 15 years in the base case of the revised version of the model. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust	Economic report TAVI	General		UK specific data from the UK TAVI dataset (BCIS) and surgical data (STCS) should surely be used in any modelling as UK data and the analysis restricted to Transfemoral TAVI. The surgical data should be restricted to isolated AVR.	Thank you for your comment. We have revised the model to use NACSA data for baseline surgery mortality risk and NICOR TAVI registry data for baseline complication risks after TAVI. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthc	Economic	General		The rate of moderate/severe PVL for TAVI used is 4.63%. This is based on data from old trials with obsolete valve types. With current generation valves the rate of moderate/severe PVL is much less. Only the following	Thank you for your comment. PVL rates were revised and now

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
are NHS Trust	report TAVI			trials involved current generation valves: PARTNER 3 Mod/Sev PVL 0.8%; Evolut Low Risk 3.4%. In the UK TAVI registry 2019/20 Mod/Sev PVL rate was 2.3% The re-intervention rate for surgery is based on a single registry study which is relatively small in size (<1000 patients), and which includes data on valves which are no longer in use and which had high rates of re-intervention, specifically the Mitroflow. This constitutes very poor evidence on which to base an important element of the economic model	come from two different studies on third generation Sapien 3 valve reporting the same rate: 2.7%. This is in line with BCIS audit reporting a rate of 3% in 2019-2020 and therefore accepted by the committee as robust data. The paper from Rodriguez-Gabella was chosen to inform baseline risk of reintervention after SAVR as it was the only one with a follow-up covering most of the time horizon of the model (13 years last follow up, time horizon 15 years). Since, the rate of reintervention increases significantly over time the length of follow-up is crucial. Using other data would have involved relying more on extrapolation. We are aware that efficiency improvements and new valves may have reduce the rate of re-intervention but looking at UK data, it does not seem that the model is over-estimating the number of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					reinterventions after surgery, at least in the short term. UK TAVI trial: 2.9% NICE model: 1.4% We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust	Evidence Review H	009 133 - 134	013 - 014 005 - 031	The data review unfortunately used older data and thus has flaws when used to assess current practice. Please use contemporary TF-TAVI data. Transapical TAVI vs surgery is not the correct comparator. Imperial has done 2 TA cases in 200 TAVI. It is a recognised access of LAST RESORT. Trans-apical access was used in 1.3% of TAVI cases (UK TAVI Registry Data, www.bcis.org.uk). It is unfair to compare TF-TAVI to TA-TAVI, or TA-TAVI to surgery. This will exclude the STACCATO trial, and parts of PARTNER 1A and 2 Trials. In addition, it is unfair to use data on Direct – aortic access TAVI (used in <0.5% of UK data and not used at all in	Thank you for your comment. The STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has now been excluded from the economic modelling based on the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Imperial.) This will exclude parts of SURTAVI and COREVALVE HIGH RISK trials. The Evidence review should have analysed the trans-femoral TAVI data separately, as has been done within all of the included trials, and within multiple previous meta-analyses. A comparison of trans-femoral TAVI and surgical AVR would be far more relevant to current practice. This was the approach taken in the ESC/EACTS and in the ACC/AHA guidelines. Rate of trans-femoral access in the trials included compared to UK TAVI registry data was as follows: PARTNER 1A 70.1%, Corevalve High Risk 82.8%, PARTNER 2 76.7%, SURTAVI 93.6%, NOTION 96.5%, PARTNER 3 100%, Evolut Low Risk 99.0%, UK TAVI Registry 96.9% The Review should give greater weighting to more contemporary trials (PARTNER 3 and Evolut Low Risk) as these are much closer to current practice, evidenced by the latest data from the UK TAVI Registry 2019-20 (www.bcis.org.uk). Both the technique of implant and TAVI Valve type has evolved reducing paravalvular leak rates significantly with the addition of "skirts" on all major vales now used. In addition, implant height is now much higher, reducing pacing rates. . The review should comment on the use of general anaesthesia vs local anaesthesia and sedation. GA means a longer procedure, slower recovery, longer hospital stay, and greater use of resources. Rate of GA in the trials included in which it was reported compared to UK TAVI registry data was as follows: Corevalve High Risk 94.6%, SURTAVI 75.7%, NOTION 81.7%, PARTNER 3 34.9%, Evolut Low Risk 56.9%, UK TAVI Registry 9.3%. This	transapical access route not being in line with current practice. The committee agrees that the proportion of transapical in these studies procedures are higher than in current UK practice. However, in line with the review protocol, the PARTNER trial data have been included as a combined data for transfemoral and transapical TAVI. Similarly, the CoreValve high risk and SURTAVI trial data cannot be excluded from the analysis post-hoc. Additionally, it would be inappropriate to exclude the CoreValve study as it is one of only few trials in the high risk cohort. TAVI route of access was included as a subgroup analysis to explore it heterogeneity was found, and not as a stratification factor in the clinical review. There were not large differences in effect estimate between the overall analysis and the transfemoral subgroup analysis. In the revised version of the health economic model, only recent trials on

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				will again affect the assessment of Length of stay and outcomes. Including "old style" TAVI disadvantages. TAVI has evolved rapidly in the last 10 years. Surgery has not advanced as rapidly.	2nd and 3rd generations valves were used to estimate relative treatment effects. Those are prevalently on transfemoral approach. As the recommendation was driven by the cost effectiveness evidence no changes have been made to the clinical review regarding the route of access as this would not affect the conclusions of the committee. It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. However, in the revised version of the health economic analysis only recent trials on new generation valves are included, so a weighting was not necessary. The committee acknowledge that the older valve types are associated with higher rates of valve complications. However, only 3 studies used 2nd or 3rd generation devices. Only the outcomes of these studies were used

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					in the health economic model to better represent contemporary practice. The committee acknowledge that general anaesthesia is required much less often for TAVI in current practice than historically. However, as above, it was not considered to be appropriate to exclude older trials from the main analysis in the clinical review.. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust	Evidence Review H	133	014	Re-intervention rates should use the last 5 years' worth of data and not older data. They should also include the fact that the TRIFECTA and MOSAIC surgical valves has high failure rate and has been widely implanted in the UK. In addition, structural valve failure classed as reintervention should separate paravalvular leak (reducing with better valves with skirts, and requiring non-major surgery) and leaflet degeneration (reducing with new generation TAVI valves).	Thank you for your comment. In terms of the clinical evidence, we could not limit data included to those trials within the last 5 years as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. The point about the possibility of a reduction in need for reintervention with more contemporary valves was discussed with the committee and incorporated into the discussion section of the evidence review. In the revised version of the model, reintervention risk ratio is calculated

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					using recent studies on 2nd and 3rd generation valves. A scenario analysis where this figure is calculated from the Evolut and PARTNER 3 only was conducted as well. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Imperial College Healthcare NHS Trust	Guideline	012	003 - 005	We as a combined unit disagree with the draft recommendation that ALL patients with severe aortic stenosis should be offered surgery as first-line treatment, with TAVI considered only for patients who are unsuitable for surgery and with non-bicuspid anatomy. This takes us back to when TAVI was only offered in the highest risk, non-surgical patients, in whom there was indeed a substantial mortality reduction from 50% at 1 year to 30% after TAVI. Removing the option of TAVI from the multi-disciplinary team seems highly inappropriate as no single risk score can calculate the risk	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				well for individual patients and replace the MDT. We feel that this recommendation may have come out of flawed economic modelling, based on historic data. The recommendations do not take any account of individual patient considerations, in particular age, life expectancy, frailty, co-morbidity, anatomical suitability for trans-femoral TAVI, and how these factors influence the best treatment options for patients. The MDT surely has the most important role in assessing the patient. There is no validated frailty score in patients facing the choice of treatments for aortic stenosis.	for people at intermediate or low surgical risk (1.5.3). The analysis was stratified by surgical risk meaning that age and co-morbidities were taken into account when assessing cost-effectiveness of TAVI (as these are the main factors driving your STS or Euroscore). Frailty is a relatively new concept in determining the feasibility of TAVI or surgery and, unfortunately, lacks any randomized trials as RCTs have been used only surgical risk. As such, frailty could not be considered in the model due to the challenges of recovering good-quality data. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability,

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Imperial College Healthcare NHS Trust	Guideline	012	003-005	It is against international guidelines that are themselves based on the same data as reviewed by NICE. 2017: European Society of Cardiology & European Association of Cardiothoracic Surgery guidelines give TAVI: 1. Class 1 indication for patients unsuitable for surgery, and for patients at high and intermediate surgical risk "with TAVI favoured in elderly patients suitable for trans-femoral access". 2. These Guidelines were produced before the publication of the Low-risk trials, and are due to be updated later in 2021, when they are likely to approve TAVI in low surgical risk patients. 2020: American College of Cardiology / American Heart Association guidelines give TAVI: 1. Class 1 indication, specifically recommending that trans-femoral TAVI is preferred to surgery in patients aged over 80, or younger with a life-expectancy of 10 years or less	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. In patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery is recommended based on shared decision-making.	
Imperial College Healthcare NHS Trust	Guideline	012	003 - 005	The recommendation does not include the role of the multi-disciplinary Heart team (MDT), let alone patient choice. The importance of the MDT is emphasised in all national and international guidance, including the British Heart Valve Society publication 'Network based care for heart valve disease' (2020), GIRFT Cardiothoracic Surgery report (2018), and ESC/EACTS 2017 & ACC/STS 2020 guidelines, as well as the NICE TAVI IPG (2017). Heart team decision-making allows complex individual patient factors to be considered. We believe that the Recommendation should be altered to refer to the importance of the MDT in deciding between TAVI and SAVR.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee agree that shared decision making is central to discussions on intervention and this has been highlighted in recommendation 1.5.1.
Imperial College Healthcare NHS Trust	Guideline	012	003 – 005 016	The Recommendation does not reflect current clinical practice. The use of OLDER data to label and assess CURRENT practice is flawed. TAVI is done in patients that may be categorised as high risk, intermediate risk, and even low risk, but in whom assessment of the individual patient by the MDT, (based on age (But not just age), life-expectancy, co-morbidities, and anatomy), suggests TAVI would be as safe and as effective as surgery, or indeed more so.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The draft consultation states that "The committee agreed that TAVI is usually reserved for when surgery is not suitable. The guidelines therefore reflect current clinical practice". This is inaccurate. At Imperial, the very strong MDT discusses 16 patients (ranging in age from under 50 to over 90) each week, with cardiac surgery, imaging, care of the elderly, and interventional specialists. IF the patient is aged at least 70 or older, and IF the patient is anatomically suitable for low-risk non-bicuspid trans-femoral TAVI, TAVI is often favoured, based on current published data and the guidelines mentioned above. We have not moved to the ACC/AHA guidance of >65 being considered for TAVI- and nor have many UK centres. TAVI is unlikely to be recommended routinely even with the current international guidelines, in UK patients under age 65, or ROUTINELY in those under 70. Average surgical age in the UK is 63 from SCTS published data, whereas average age for TAVI in the UK is 81 (UK TAVI Registry data). Thus surgical and TAVI patients are different and will remain different with evolving practice.	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Imperial College Healthcare NHS Trust	Guideline	012	003 – 005	TAVI does not reduce the need for Surgery, but expands the indication for TAVI, and the drive to expand access for TAVI has increased the referral base for Severe Symptomatic AS, a condition with a prognosis worse than cancer. We do over 200 TAVI per year, without a reduction in the surgical program in that time that TAVI has grown from 50 to 200/year. The surgical patients not the same as the TAVI patients- and both surgical and TAVI programs have excellent audited results, as a consequence of choosing the correct patients for each treatment. TAVI has increased through appropriate heart team guided recommendation of TAVI in low and intermediate risk older patients.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					(short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Imperial College Healthcare NHS Trust	Guideline	012	003 – 005	Had TAVI not been available during the COVID crisis, many of these patients would have died waiting for a surgical alternative. The Recommendation does not reflect current post-COVID clinical practice with us at Imperial or nationally. It would not be possible for surgery to deliver the increased demand that would result from implementing these draft recommendations and patients would face huge waits and many would die on the waiting list. Published registry data show that the mortality on a waiting list for surgery is about 4% per month. (Malaisrie, Ann Thorac Surg 2014)	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Imperial College Healthcare NHS Trust	Guideline	012	003 – 005	Where is patient choice? The draft guideline gives no consideration to patient experience and patient preference. TAVI is performed under local anaesthetic, has a median hospital stay of 2-3 days, and immediate recovery. Surgery is highly invasive, involving chest incision, general anaesthetic, intensive care stay, median stay of 8 days in total, and recovery period of 3-6 months, especially in older patients. TAVI is therefore a far preferable experience for patients. Patient preference should always be a factor in clinical decision-making.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The committee agree that shared decision making is central to discussions regarding interventions and highlight this in recommendation 1.5.1. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. TAVI
Imperial College Healthcare NHS Trust	Guideline	012	003 – 005	The committee did not include any patient representation. The failure to include patient representation may explain the failure to give sufficient focus to patient preference and patient experience. Please see this article on patient experience from Rod Gilchrist- who had a day case TAVI at the height of COVID. https://www.telegraph.co.uk/authors/r/roderick-gilchrist/	Thank you for your comment. There were two lay members on the committee with lived experience. We have highlighted the importance of shared decision making in recommendation 1.5.1 and 1.9.1. The latter also makes a cross referral to the NICE guideline on patient experience in adult NHS services.
Imperial College Healthcare NHS Trust	Guideline	012	003 – 005	The COVID effect has not been considered. Imperial has to suspend cardiac surgery in 2020 due to COVID. TAVI in low risk patients proved to be highly effective and saved lives. The waiting lists for surgery remain. The draft recommendations as worded may BLOCK access to TAVI that the MDT recommends as a reasonable alternative to surgery. TAVI had no requirement for ICU, and hospital stay is far shorter. Our internal data is	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				consistent with the UK data, but we managed to perform >200 TAVI in the COVID year from April 2020, maintaining a service using the independent sector and day-case TAVI, to avoid deaths on the waiting list. Between March and October 2020 in the UK there were 3196 fewer SAVRs than expected, and 1431 fewer TAVIs. (Martin et al. Circ Intervent. In press). TAVI allows patients to be treated quickly, with short hospital stays, and no use of ICU. This is surely vital to maintain ITU capacity for more essential surgery where there is no other evidence based intervention?	unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Length of hospital stay was included in the health economic model (see evidence review H). NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account. TAVI

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Imperial College Healthcare NHS Trust	Guideline	012	006 – 007	Bicuspid valve treatment is not routine with TAVI, but should be allowed if the MDT agrees the plan. Imperial have saved recently a 52 year old and a 60 year old that were turned down for surgery. We feel surgery is still 1st line in young, fit, active low risk bicuspid valve patients under the age of 70, However, over 70, the MDT should be empowered to make the recommendation of TAVI if appropriate. The draft guideline allows no recommendation for TAVI in patients with bicuspid anatomy who are unsuitable for surgery. This is inappropriate. Forrest (2020) reported outcomes of tricuspid versus bicuspid disease treated by TAVI in the TCT registry, and showed no difference in mortality or stroke at 30 days or 12 months. TAVI in bicuspid anatomy is in routine use in the NHS. Medical therapy for AS is associated with very poor survival. TAVI should be recommended in preference to medical therapy for bicuspid disease.	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included studies meeting the review protocol criteria (see Appendix A). In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.
Imperial College Healthcare NHS Trust	Guideline	General	General	Imperial College Healthcare NHS Trust is one of the largest tertiary centre trusts in the UK and is a cardiac surgical centre, offering a broad range of adult cardiology and cardiac surgery interventions, including TAVI, PFO closure, MitraClip, LAA closure, Surgical Aortic (AVR) and Mitral valve replacements (MVR), including minimal access surgery. Severe Symptomatic Aortic Stenosis (SSAS) has a prognosis worse than cancer, and TAVI and AVR are complementary therapies. We feel that incorrect assumptions in the costings especially of TAVI procedures has lead to over aggressive recommendation of AVR over TAVI. In addition, no mention has been made of choice of surgical AVR, which is relevant due to the recent issues with Trifecta and Mitraflow valves.	Thank you for your comment. We revised the economic model based on stakeholder comments to reflect contemporary costs and outcomes of modern valves including the need of ICU facilities and LOS. The cost estimated for TAVI (around £5,500) now compares well with the cost reported from several Trusts during the consultation. TAVI became cost effective for high risk people but remains non-cost effective at the current valve list price for people at

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Finally, the absence of a recommendation for Functional mitral regurgitation treatment with edge to edge repair is again due to financial modelling, is incorrect.	intermediate or low surgical risk (1.5.3). In relation to choice of surgical AVR, only the invasiveness of surgery was considered in the review protocol and comparisons between different types of surgical valve were not included. Therefore recommendations regarding the type of surgical aortic valve could not be made. The model demonstrated that transcatheter mitral valve repair had a low chance of being cost effective at £20,000 per QALY gained, with an incremental cost-effectiveness ratio of £30,000 per QALY gained. These results are in line with the UK study identified in the literature review. The health economic model was largely based on results from the COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over medical management.
Leeds Teaching Hospital NHS Trust	Comments re COVID-19	General	General	Cancellations and access to critical care with respect to COVID-19. The TAVI service has been one of the success stories of COVID in Leeds. The ability to offer high quality aortic valve intervention without using critical care resources and with short hospital stays meant that the TAVI service was resistant to some of the pressures exerted by COVID-19. Very few TAVI procedures were cancelled because of bed pressures in fact TAVI increased from 323 (2019) to 392 (2020). In our centre SAVR outcomes have been outstanding with all-comer 30-day mortality of 0.6% in the past 8 years. Our heart team has had real concerns about critical care capacity and overall surgical output was down 42% in 2020 compared to pre-COVID years. Cancellation of any procedure is associated with costs: wasted resource; unplanned readmission; conversion of a stable low risk patient to a less stable acute patient; and harm (including death and disability). The impact of cancellation for patients psychologically and emotionally is also significant. Our local data suggest that surgical aortic valve replacement (SAVR) as a service requires a substantial increase in resources: anaesthetists, ODPs, theatre nurses, ITU beds, ITU nurses, and ITU physicians. If SAVR is to be the default strategy for every operable patient, as the current NICE draft guidance suggests, a very significant increase in	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				resources would be required and these costs are not currently accounted for in the cost-utility analysis. In addition, the impact of COVID-19 and pressure on critical care is not described or modelled in the proposed guideline, as the prevalence of the disease varies in the population with intermittent outbreaks, critical care may come under further pressures, adversely affecting the ability to offer SAVR.	effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital NHS Trust	Economic report TAVI	001 Introduction	018	The NHS Reference costs are quoted (excluding valve costs) for TAVI and SAVR, the TAVI procedural costs quoted range between £6000 and £9000. We analysed patient-level hospital costings data (PLICS analysis) for the past 10 consecutive elective cases performed in Leeds. The mean cost per procedure was £5,322. We believe that many of the perceived costs of the procedure relate to bundling of general anaesthesia, critical care and hospital length of stay. Our default strategy for TAVI in Leeds in the past 5 years has been to avoid general anaesthesia and critical care. Our use of general anaesthesia for the past 1000 cases has been 7.7%, this includes 205 acute or emergency TAVIs in patients who were clinically unstable and 50 patients requiring surgical cutdown (to the chest wall, subclavian or carotid artery). In short, a default strategy of non-GA percutaneous trans-femoral approach obviates the need for an anaesthetist, ODP, anaesthetic recovery, trans-oesophageal echocardiography, critical care bed occupancy and lengthy hospital stay. We believe that the TAVI reference procedural costs in the model should be adjusted accordingly.	Thank you for your comment. The cost of a TAVI procedure excluding LOS, ICU and valve cost is estimated to be £4,500. If we add the ICU and hospital LOS which were revised to accurately reflect the UK settings, we estimate a cost ranging from £5,470 to £5,570, which is very similar to the cost provided by your institution. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital NHS Trust	Economic report TAVI	009 Long-term model	2.2.1.2	We do not feel that a 30-year time horizon for the long-term outcomes Markov model is appropriate for TAVI. The average age of patients treated in our centre is 79, the average age in the UK TAVI trial was 81 and the average age from the UK TAVI registry is 80 (data accurate up to 2020). We feel that a 10-year time horizon is more realistic. A minority of 'younger' patients are treated by TAVI, however those patients treated at a younger age carry much higher co-morbidity and a shorter life expectancy. The relative survival of the younger patients is consequently much lower than of more elderly patients. These data are shown by figures 3,4,5 in the modelling document and are summarised in the paper from which these data are provided (Martin et al, ref 18 in long term model) Martin et al. J Am Heart Assoc. 2017;6(10):e007229.	Thank you for your comment. The committee agreed to reduce the time-horizon in the base case scenario to 15 years. This should reflect the average life expectancy of 75 years old TAVI patients, who now populate the low surgical risk category. A period shorter than 15 years was considered inappropriate as some of the consequences of TAVI, such as the higher need for reintervention, would occur later. Nevertheless, several scenario analyses were conducted showing the cost-effectiveness results using different time horizons: 5, 10, 15 and 30 years.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital NHS Trust	Economic report TAVI	014	Table 2	The risk of moderate/severe paravalvular leak (PVL) is quoted at 4.63%. This outcome drives cost in the subsequent economic modelling. We have concerns that this figure is made from historical data with old generation heart valves (now not used) that were associated with higher risk of PVL. The most contemporary data with the newest generation heart valves demonstrate much lower rate of important PVL (self-expanding 3.5%, balloon expanding 0.8%) (1,2). The data from the UK TAVI study (a non-industry funded all-comers randomised controlled trial (in the public domain presented at PCR London Valves conference 2020) is probably the best and most contemporary source of data, the rate of moderate paravalvular leak being 2.3% in TAVI arm v 0.6% in SAVR arm. We have general concerns that the economic model has not included the most contemporary randomised controlled trials: the Evolut low risk trial (1),	Thank you for your comment. We updated our model to use data for PVL that reflects the outcomes of new generation valves (SAPIEN 3). The new rate we use for moderate and severe PVL is 2.7%, which is very close to the percentage reported in the last BCIS audit for TAVI in 2019/20 for moderate and severe PVL (3%). Evolut and Sapien 3 low risk trials have been included in the meta-

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the Sapien 3 low risk trial (2) and the UK TAVI allcomers trial (3) (reflecting the use of valves currently in practice) We feel that the cost utility model should be adjusted to reflect these more recent data. (1) Popma JJ et al. NEJM 2019;380:1706-15. (2) Mack MJ et al. NEJM 2019;380(18):1695-1705. (3)Toff et al ePCR London valves Nov 2020	analysis informing the treatment effects used in the model. UK TAVI trial could not be included as it is still unpublished, although its descriptive statistics on length of hospital stay and ICU stay have been extracted and used in the model. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital	Economic report TAVI	015	Table 2	Pacemaker implantation risk ratio of TAVI v SAVR is quoted at x2.43. In our own centre using contemporary techniques and modern valves the PPM rate is 9%, this is in line with the data from the UK TAVI trial where PPM after TAVI was 12.2% and after SAVR 6.6%. Using these data, a ratio of x1.8 would seem more accurate to the model.	Thank you for your comment. We have now updated our complications baseline risks to reflect contemporary UK practice. The PPM

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Trust					rate is now informed by the UK NICOR TAVI audit and it is 9.7%, which is very close to the percentage reported in your institution. The new risk ratio used is 1.8 (TAVI vs SAVR) which was calculated through a meta-analysis of PARTNER 2, PARTNER 3 and Evolut. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital	Economic report TAVI	016	Table 2	Regarding the costs related to patient length of stay in hospital and ICU. We feel that these costs (for TAVI in particular) are very inaccurate. Our local data for continuous unselected patients in the past 3 years is that 1% of patients were admitted to ITU. In fact, very few patients required even a	Thank you for your comment. After further discussion, the committee agreed to use UK data for

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Trust				level 2 (CCU/HDU) bed. Our default strategy for all elective patients in the past 3 years has been a standard hospital bed with portable telemetry if required. In our centre 70% patients are discharged within 2 days, 40% within 1 day. The median day of discharge for all patients (all levels of risk and acuity) being 2 days in the past 4 years. These outcomes are reflective of a modern approach in a heart valve centre of excellence with no sacrifice in safety or quality and are becoming a benchmark standard. The cost utility model should be adjusted to reflect standards achieved in a heart valve centre of excellence, specifically removing all costs relating to ITU/critical care and adjusting the length of hospital down to 2 days for elective cases.	Length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. LOS ranges from 3 to 3.3 in TAVI. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital NHS Trust	Economic report TAVI	017	Table 2 Valve costs	The analysis uses TAVI valve costs as quoted in the NHS supply chain catalogue. Until recently we sourced our TAVI valves internally (not under the umbrella of NHS supply chain). At that time, we were able to source our valves at a significantly lower price: for example, Portico self-expanding valve £12000, Evolut R £14300, Evolut Pro £17000. We would challenge the price quoted in the model as being well above the actual valve costs. We further note that in the cost effectiveness analysis of the UK TAVI study (presented at ePCR London valves Nov 2020) the unit price for a TAVI valve was £17500, sourced from NHS supply chain. The valve cost is the	Thank you for your comment. In the base case scenario, the price of the valve is now set at £17,500 as this is the average price 80% of all TAVI under the NHSE High-Cost Tariff Excluded Devices Programme. We are aware that there is heterogeneity in the price across valves and NHS centres but the price sourced from

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				single largest cost for the TAVI treatment arm, so it is critical to build in these costs accurately and plan for adjustments of costs long term.	NHS Supply Chain is an average and is consistent with that used in the UK TAVI trial study. The cost of the valve is indeed the most critical aspect of this model and, therefore, a threshold analysis was conducted to asses the price that would make TAVI cost-effective for each risk category. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital	Economic report TAVI	021	Table 6 Risk of Inter	The reintervention odds ratio calculated from a meta-analysis of old generation TAVI valves (none of which are now used) seems disproportionately high. We note that this paper (Let et al 2020, reference 13 in the model) was actually excluded from the evidence review in another part of the NICE draft guideline due to 'methods are not adequate/unclear'	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review which did not meet the review

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Trust			vention	The Odds ratio of reintervention TAVI v SAVR is calculated at x3.5 in every year up to year 5. This model is just not reflective of contemporary practice. Our experience in Leeds from our whole population treated by TAVI since 2008 (2200 patients) is that subsequent to the index TAVI procedure: 4 valves degenerated (3 re-treated by TAVI, 1 treated by valvuloplasty), 3 patients were successfully re-treated for para-valvular leak subsequent to the index implant (2 with further TAVI valves and 1 with a vascular plug device, and 3 patients were treated with SAVR after TAVI was abandoned after the initial procedure. One other patient received coronary artery by-pass surgery after a successful TAVI. We calculate that the reintervention rate from our whole series (2008-2021, n=2200) is 11 patients (<0.5%). The meta-analysis used in the NICE model (Ler et al 2020) quote 33 re-interventions in early generation TAVI patients (1%) v 4 re-interventions in 807 SAVR patients at 5 years (0.5%). Even from these historic data the odds ratio should be adjusted down from x3.5 to x2, and this should be over a 5-year period and not annualised. Furthermore, from our real-world data, the reintervention rate for TAVI is 11/2200 (0.5%) the same as the pooled surgical data published in the meta-analysis. This would give a neutral effect on reintervention on the cost utility analysis (Odds ratio of 1) Ler A et al. J of Cardiothoracic Surgery. 2020; 15(1):127	protocol criteria (see appendix A in evidence review H), though it was included as an evidence for the model. After further discussion, the committee agreed to exclude this evidence as it was clearly focused on old generation valves not reflecting contemporary practice, as your comment highlighted. Relative treatment effects for reintervention now come from the trials included in the literature review as these were extensively discussed and reviewed by the committee. In the base case analysis, we are only using the treatment effect captured in trialsevaluating 2nd and 3rd generation valves: • PARTNER 2 • PARTNER 3 • EVOLUT In addition, there is a sensitivity analysis where this figure is instead

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					calculated from Evolut and Partner 3 only, with a relative risk close to 1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Leeds Teaching Hospital NHS Trust	Guideline	001 023	General 008 025 - 026	1.1.3 The draft NICE guidance explicitly aims "to improve diagnosis and raise awareness of the indications for intervention. The present challenges are the under-diagnosis of significant heart valve disease, delayed referral for expert assessment and the duration of the treatment pathway (time to treatment) for patients with severe symptomatic heart valve disease." (page 1, line 8). We feel that these aspects have been insufficiently addressed in the draft NICE guidance. Improved detection must be achieved by better access to echocardiography for "at risk groups" such as breathless patients, patients with Atrial Fibrillation or patients above the age of 75 (where >10% patients	Thank you for your comment. We now refer to atrial fibrillation and people aged 75 yrs and over in recommendation 1.1.1

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				will have significant heart valve disease) especially in primary care. (see British Heart Valve Society (BHVS) service delivery recommendations (1). This target requires increased resource for echo provision and cardiac physiology this does not reflect current practice as stated on page 23, line 25 + 26. We suggest that this is corrected to enable increased resources to be provided. (1) https://www.bhvs.org.uk/bhvs-blueprint	
Leeds Teaching Hospital NHS Trust	Guideline	005	General	1.1.6 'Referral to a specialist' does not explicitly describe expert valve clinic with embedded imaging and access to multiple disciplines. Assessment and surveillance of patients with heart valve disease requires healthcare professionals with appropriate competency and is best done in the setting of a heart valve clinic according to standard surveillance guidelines as part of network-based care for heart valve disease. Heart valve clinics improve implementation of guidelines at lower cost than general cardiology clinics leading to earlier recognition of symptoms and improved outcomes. Treatment of patients is best done in heart valve centres of excellence. Standards have been recommended by the European Society of Cardiology. (1-4) In Leeds we successfully have developed a multi-disciplinary heart valve clinic that offers all aspects of care for patients with heart valve disease including diagnosis, surveillance and referral for treatment. We feel that the NICE guidance should explicitly recommend the concept of heart valve clinics and heart valve centres of excellence in their document as these are vital to offer high quality care to patients with heart valve	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				disease. Omission of these important concepts in the care for patients with heart valve disease will limit the implementation of any NICE guideline. 1 European Heart Journal (2017) 38, 2739–2791 2 Taggu W, Topham A, Hart L, et al. A cardiac sonographer led follow up clinic for heart valve disease. Int J Cardiol. 2009; 132: 240-243. 3 Ionescu A, McKenzie C, Chambers J. Are valve clinics a sound investment for the health service? A cost-effectiveness model and an automated tool for cost estimation. OpenHeart 2015; 2: e000275. Doi:10.1136/openhrt-2015-000275 4 Zilbersac R, Lancellotti P, Gilon D, et al. Role of a heart valve clinic programme in the management of patients with aortic stenosis. Eur Heart J CVI 2017; 18: 138-44.	
Leeds Teaching Hospital NHS Trust	Guideline	005	004	Excess waiting times for patients with severe symptomatic heart valve disease cause avoidable harm. The prognosis of untreated severe aortic stenosis is worse than most cancers. The mortality for patients awaiting aortic valve intervention is 4% per month.(1) Local data in Leeds has shown an average wait for patients with severe symptomatic aortic stenosis from referral to treatment (by TAVI) of 6 months for out-patients and 4 weeks for in-patients (2019). Every year patients die while on an assessment/treatment pathway that is overlong. The NICE draft guidance does not address time to assessment and time to treatment sufficiently.	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We feel that all patients with suspected severe symptomatic heart valve disease should have expert assessment and echocardiogram within 2 weeks (similar to rapid heart failure assessment, rapid access chest pain clinic and suspected cancer) and not 4 weeks as stated in the guidance (page 5, line 4). We feel that NICE should endorse a referral to treatment target of 10 weeks (similar to NHS cancer targets). These interventions in our view would help reduce the harm as a result of excessive waiting times suffered by patients with severe symptomatic heart valve disease in the NHS. (1) Malaisrie et al. Ann Thorac Surg 2014 ;98(5) :1564-70.	
Leeds Teaching Hospital NHS Trust	Guideline	012 038	003 - 006 017	Empowerment of the patient is mentioned in the first line of the recommendation (page 4). However, the body of the guidelines makes little reference to informed patient choice, local expertise and the pooled knowledge of local experienced heart team. The draft NICE guidelines are therefore at substantial variance to international guidelines on valvular heart disease that have given emphasis to a collegiate approach from a heart team and put the patient central to decisions on their own treatment. Secondly, the guidelines badly misjudge the current practice of aortic valve intervention in the UK, where TAVI is used widely in certain patient groups. The 2017 European Society of Cardiology & European Association of Cardiothoracic Surgery guidelines give TAVI a Class 1 indication for patients unsuitable for surgery, and for patients at high and intermediate	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). The recommendation highlighted in your comment emphasises the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				surgical risk "with TAVI favoured in elderly patients suitable for trans-femoral access". The 2020 American College of Cardiology / American Heart Association guidelines give a Class 1 indication for TAVI, specifically recommending that trans-femoral TAVI is preferred to surgery in patients aged over 80, or younger with a life-expectancy of 10 years or less, and that in patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery is recommended based on shared decision-making. The proposed NICE recommendations do not take any account of individual patient considerations, in particular age, life expectancy, frailty, co-morbidity, anatomical suitability for trans-femoral TAVI, and how these factors influence the best treatment options for patients. The recommendation does not include appropriate reference to the role of the multi-disciplinary Heart team (MDT), and shared decision-making. The importance of the MDT is emphasised in all national and international guidance, including the British Heart Valve Society publication 'Network based care for heart valve disease' (2020), GIRFT Cardiothoracic Surgery report (2018), and ESC/EACTS 2017 & ACC/STS 2020 guidelines, as well as the NICE TAVI IPG (2017). Heart team decision-making allows complex individual patient factors such as those outlined above to be considered.	(short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). See evidence review H. NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We believe that the recommendation should be altered to refer to the importance of the MDT in deciding between TAVI and SAVR. This practice is endorsed and used consistently in our centre. A prime example of this is page 38 line 17- surgery for aortic stenosis. Our practice in Leeds, consistent with international guidelines and contemporary evidence is that when surgery is high risk, or intermediate risk in an elderly patient over 80 years TAVI is usually offered (not surgery). The assumptions that the committee make about current practice in the UK are simply not true in our centre.	The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Leeds Teaching Hospital NHS Trust	Guideline	012 037 038	006 - 007 011 - 013 003 - 007	TAVI for bicuspid valve aortic stenosis. Our heart team offers to TAVI to patients with bicuspid aortic stenosis who are unsuitable for SAVR. This patient group comprises 10% of our caseload and the clinical outcomes with TAVI are not significantly different to the 'non-bicuspid' patients. We feel that the proposed NICE guideline is unduly negative on the outcomes for TAVI in bicuspid aortic stenosis, this belief is based on our local experience and the presence of high quality, albeit non-randomised, registry studies. We do not believe that palliative care (as suggested in the guideline) is an ethical option for patients when a highly effective evidence-based therapy is available and surgical AVR is unsuitable. Forrest et al: TVT registry (TAVI in bicuspid AS v TAVI in tricuspid AS) equally low rates mortality, stroke, no difference between two types of aortic stenosis for safety / efficacy	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated. The recommendation does not prevent an MDT to consider TAVI in patients presenting with bicuspid aortic stenosis if age and comorbidities preclude surgery.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Elbadawi et al: Propensity matched study (TAVI v SAVR for bicuspid AS) no difference in mortality or safety outcomes, shorter hospital stays for TAVI. Forrest JK et al. JACC CVI 2020;13(15):1749-1759. Elbadawi A et al. JACC CVI 2019;12(18):1811-1822	
LivaNova	Guideline	011	007	LivaNova supports the list of parameters to include when deciding on an intervention; "Include in the discussion: • the benefits to quality of life (both in the short and long term) • valve durability • the risks associated with the procedure • the type of access for surgery (median sternotomy or minimally invasive surgery) the possible need for other cardiac procedures in the future"	Thank you for your comment.
LivaNova	Guideline	011	013	Although there is reference to "shared decision making", LivaNova suggests that "via a multidisciplinary team (MDT)" be added as decisions about interventions should be made in collaboration with a multi-disciplinary team (MDT) which may include, but is not limited to, healthcare professionals (HCP) expert in cardiac surgery, cardiology, cardiac imaging and anaesthesia. The MDT approach is recognised in current guidelines[1,2]. 1. Baumgartner H. et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease European Heart Journal (2017) 38, 2739–2791	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Otto CM et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, J Am Coll Cardiol. 2021 Feb 2;77(4):450-500. doi: 10.1016/j.jacc.2020.11.035	
LivaNova	Guideline	011	018	LivaNova supports the statement that "if minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre".	Thank you for your comment.
LivaNova	Guideline	011	018	LivaNova suggests adding the following sentence: "Sutureless bioprostheses may facilitate minimally invasive surgery and should be considered in minimally invasive aortic valve replacement". This statement is supported by the results of a recent randomised controlled trial [1], prospective real-world registry data[2], consensus papers[3,4] and large case series[5] and it is also reflective of current clinical practice. For clarity, the paragraph would therefore read: "When surgery is agreed, base the decision on the type of surgery (median sternotomy or minimally invasive surgery) on patient characteristics and patient preferences. Sutureless bioprostheses may facilitate minimally invasive surgery and should be considered in minimally invasive aortic valve replacement. If minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre." 1. Fischlein T. et al. Sutureless versus conventional bioprostheses for aortic valve replacement in severe symptomatic aortic valve stenosisJ Thorac Cardiovasc Surg. 2021 Mar;161(3):920-932	Thank you for your comment. The review protocol did not specify sutureless bioprosthesis as part of the sub-group analysis (see appendix A evidence review H) and the committee were therefore unable to make a recommendation. Subgroups were chosen by the committee based on the most clinically probable cause of any heterogeneity identified.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. Glauber M. et al. Minimally Invasive Aortic Valve Replacement with Sutureless Valves: Results From an International Prospective Registry. Innovations (Phila). Mar/Apr 2020;15(2):120-130) 3. Gersak B. et al. Sutureless, rapid deployment valves and stented bioprosthesis in aortic valve replacement: recommendations of an International Expert Consensus Panel. Eur J Cardiothorac Surg. 2016 Mar;49(3):709-18 4. Glauber M et al. International Expert Consensus on Sutureless and Rapid Deployment Valves in Aortic Valve Replacement Using Minimally Invasive Approaches. Innovations (Phila). 2016 May-Jun;11(3):165-73 Solinas et al. Right anterior mini-thoracotomy and sutureless valves: the perfect marriage. Ann Cardiothorac Surg 2020;9(4):305-313	
LivaNova	Guideline	012	003	LivaNova supports the indication to "offer surgery, if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease". LivaNova suggests to further clarify the different options available for surgical aortic valve replacement by modifying the sentence as follows: "Offer surgical aortic valve replacement (mechanical and biological including sutureless bioprostheses), if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease". This is consistent with the literature contained in Evidence review H-Interventions[1] that included studies with both sutured and sutureless aortic	Thank you for your comment. Type of valve was included as a subgroup in in appendix A evidence review H. However, this subgroup analysis did not explain any observed heterogeneity for outcomes where this existed. The committee were therefore unable to make recommendations on specific valve types.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				bioprosthetic technologies and IPG 624 Sutureless aortic valve replacement for aortic stenosis (2018)[2] that states "Current evidence on the safety and efficacy of sutureless aortic valve replacement for aortic stenosis is adequate to support the use of this procedure, provided that standard arrangements are in place for clinical governance, consent and audit". 1. H. Evidence review for transcatheter intervention, surgery or conservative management in heart valve disease. Available at https://www.nice.org.uk/guidance/GID-NG10122/documents/evidence-review-8 Sutureless aortic valve replacement for aortic stenosis (2018) Available at https://www.nice.org.uk/guidance/ipg624	
LivaNova	Guideline	012	016	LivaNova supports the indication to "offer surgical mitral valve replacement to adults with rheumatic severe mitral stenosis if transcatheter valvotomy is unsuitable". LivaNova suggests to further clarify the different options available for mitral valve replacement, and modify the sentence as follows: "Offer surgical mitral valve replacement (**either with mechanical or biological prostheses**) to adults with rheumatic severe mitral stenosis if transcatheter valvotomy is unsuitable".	Thank you for your comment. Type of valve was included as a subgroup in in appendix A evidence review H. However, this subgroup analysis did not explain any observed heterogeneity for outcomes where this existed. The committee were therefore unable to make recommendations on specific valve types. Nevertheless, recommendation 1.5.1 covers discussion of prosthetic valve durability during the decision process for people requiring valve intervention.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
LivaNova	Guideline	013	004	LivaNova supports the recommendation to offer surgical mitral valve repair (by median sternotomy or minimally invasive surgery) to adults with severe primary mitral regurgitation and an indication for repair, if surgery is suitable.	Thank you for your comment.
LivaNova	Guideline	013	007	LivaNova supports the indication to "offer surgical mitral valve replacement (by median sternotomy or minimally invasive surgery) to adults with severe primary mitral regurgitation and an indication for surgery, if the valve is not suitable for repair and surgery is suitable". LivaNova suggests to further clarify the different options available for mitral valve replacement, and modify the sentence as follows: "Offer surgical mitral valve replacement, **either with mechanical or biological prostheses,** (by median sternotomy or minimally invasive surgery) to adults with severe primary mitral regurgitation and an indication for surgery, if the valve is not suitable for repair and surgery is suitable.	Thank you for your comment. Type of valve was included as a subgroup in in appendix A evidence review H. However, this subgroup analysis did not explain any observed heterogeneity for outcomes where this existed. The committee were therefore unable to make recommendations on specific valve types. However, recommendation 1.5.1 covers discussion of prosthetic valve durability during the decision process for people requiring valve intervention.
LivaNova	Guideline	013	018	LivaNova supports the recommendation to consider surgical mitral valve repair (by median sternotomy or minimally invasive surgery) for adults with severe secondary mitral regurgitation and an indication for surgery, if surgery is suitable.	Thank you for your comment.
LivaNova	Guideline	013	021	LivaNova supports the indication to "consider surgical mitral valve replacement (by median sternotomy or minimally invasive surgery) for adults with severe secondary mitral regurgitation and an indication for surgery, if the valve is not suitable for repair and surgery is suitable".	Thank you for your comment. Type of valve was included as a subgroup in appendix A evidence review H. However, this subgroup analysis was not performed as there was no

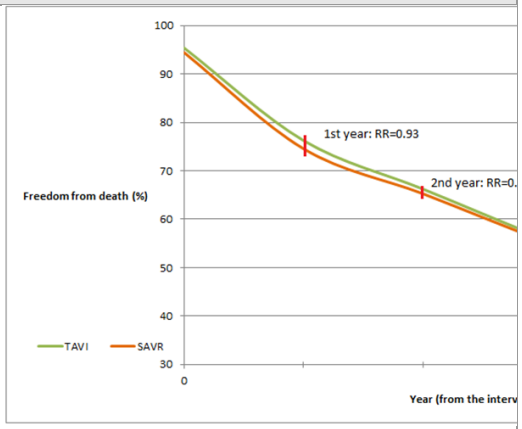
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				LivaNova suggests to further clarify the different options available for mitral valve replacement, and modify the sentence as follows: "Consider surgical mitral valve replacement, **either with mechanical or biological prostheses** (by median sternotomy or minimally invasive surgery) for adults with severe secondary mitral regurgitation and an indication for surgery, if the valve is not suitable for repair and surgery is suitable".	heterogeneity in the studies. The committee were therefore unable to make recommendations on specific valve types. Nevertheless, recommendation 1.5.1 covers discussion of prosthetic valve durability during the decision process for people requiring valve intervention.
LivaNova	Guideline	035	022-024	LivaNova suggests modifying the following paragraph: "Minimally invasive surgery **will not** be suitable for **most patients**. Those for whom it is suitable may decide not to opt for a minimally invasive surgery *after considering the increased likelihood of failure of repair, needing redo surgery or other complications*". LivaNova request for the first sentence to be reworded and the last part of the paragraph to be removed as recent randomised controlled trial data included in Evidence review H- Interventions[1] is generally balanced for outcomes with respect to standard versus minimally invasive approaches. For clarity, the requested amended paragraph would read as follows: "Minimally invasive surgery **may not** be suitable for **all patients**. Those for whom it is suitable may decide not to opt for a minimally invasive surgery". H. Evidence review for transcatheter intervention, surgery or conservative management in heart valve disease. Available at https://www.nice.org.uk/guidance/GID-NG10122/documents/evidence-review-8	Thank you for your comment. The wording of this paragraph has been amended slightly to better reflect the evidence identified in the review.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
LivaNova	Guideline	035	009	LivaNova supports the list of parameters the committee highlighted for consideration when discussing interventions; "Specifically, the committee highlighted valve durability, the risks associated with the procedure and the possible need for other cardiac procedures in the future."	Thank you for your comment.
Liverpool Heart and Chest NHS Trust	Economic report	022	013	The report states that the clinical review found no long term improvement in TAVI compared to SAVR, but a NICE conducted meta-analysis of the 6 included RCT's found TAVI to show a moderate improvement in mortality in the year following the intervention; as demonstrated in Figure 7.	Thank you for your comment. The clinical review pooled together all trials using the last follow-up available and found no improvement in mortality. For the economic model, time-dependent treatment effects were calculated as, during the first year, TAVI showed a survival benefit (see the graph):

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					
Liverpool Heart and Chest NHS Trust	Economic report	023	004	Table 7 relative treatment effects. These figures are not representative of contemporary UK (or international) practice, as evidenced UK TAVI Trial, and NICOR TAVI database. The intervention odds ratio for TAVI vs SAVR is stated as 3.52 in the first year, and 3.55 thereafter. Those reintervention assumptions, as currently modelled using the Ler 2020 paper, have particular impact on the lifetime cost of TAVI, yet in Evidence Review 8, Appendix 1, it states that Ler 2020 is excluded from analysis on the basis that 'methods are not adequate/unclear'. Somewhat surprisingly that this would form such a prominent role in determining costs.	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review not using GRADE system, though it was included in the model as the absence of GRADE system was not considered a big limitation. After further committee discussion, it was agreed to exclude this evidence as it was clearly focused on old generation valves not reflecting contemporary

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					practice, as highlighted in your comment. NICOR data is now used for baseline probabilities after TAVI whereas UK TAVI trial was used to inform hospital LOS and ICU after TAVI or surgery. Relative treatment effects for reintervention now come from the trials included in the literature review as these were extensively discussed and reviewed by the committee. In the base case analysis of the model the treatment effect was only from trials evaluating 2nd and 3rd generation valves. In a sensitivity analysis only trials of 3rd generation valves were used. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	025	034	The report states: "Additionally, the TAVI cost reported in the NHS Reference Costs does not include the cost of staying in an intensive care unit (ICU) after the intervention which, as the trials in the clinical review show, tend to be an important component of the total cost of the intervention". This is wholly incorrect when considering contemporary UK practice, which reports a median ITU bed stay of 0 days. Our own data (LHCH audits which can be made available on request) also show a median bed ITU stay of 0 days.	Thank you for your comment. It has now been decided to use descriptive statistics from the UK TAVI trial to inform Length of hospital stay and ICU stay after TAVI and surgery in the model. In this study the median ICU stay after TAVI was 0, and the model is now using this figure when calculating the cost of the procedure. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	026	021	Table 11 demonstrates costs of intervention. It lists TAVI high risk TF as £7681, and low risk TF as £6006. **[This text was identified as confidential and has been removed].**	Thank you for your comment. We are unfortunately unable to use confidential information as all the data for the model must be taken from published sources as outlined in the NICE manual. The length of hospital stay and ICU stay have been revised using UK TAVI trial data. The cost of a TAVI procedure for each risk group (without the valve) was estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	027	012	Table 12 provides the LOS and ITU stays used in the model for TAVI and SAVR, citing Partner 1 and 2 trials. AS explained above, these figures are simply not representative of UK practice. The NICOR TAVI database which is in the public domain, shows an ITU LOS of 0 days, and a median LOS of 3 days.	Thank you for your comment. The committee agreed that these figures are not representative of UK practice and so the ITU and hospital LOS figures have now been substituted with figures coming from UK TAVI trial showing the same numbers that you quote. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	028	006	Table 14 shows hospital ward stay costs. It is hard to explain why TAVI has a higher weighted average ward stay of £473 compared to a SAVR ward stay of £325, despite both ITU and ward stay being greater for SAVR in table 12?	Thank you for your comment. It is likely that in the UK, TAVI patients are, on average, sicker and therefore require more medical care, although in the model that the patients in the SAVR and TAVI arms should be identical. Therefore, it has been decided to now use the same average ward stay cost for both SAVR and TAVI: £325. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	033	001	Table 21: Cost of pacemaker. It would appear that these reference costs were simply added in full, including hospital stay, to the TAVI or SAVR costs. If these costs are already represented as extra bed stays in the TAVI tariff then they should not be additive.	Thank you for your comment. The committee discussed whether these costs should or should not account for separately in the base case scenario. It was agreed in the end, that the cost of a pacemaker implantation and, in particular, its length of stay component was already captured in the intervention HRG and therefore this cost as well as of the other short-term event costs have now been removed from the base case analysis. There is now a sensitivity analysis where these costs are still added. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	042	019	Table 30: Events for 1000 patients. None of these event rates are recognisable and appear grossly inflated. For example, re-intervention for TAVI is quoted as 203 patients per 1000, 20.3%? This MUST be an error. Vascular complications 8.7%. CVA 6.1%, hospitalisation 106%? The re-intervention rate (TAVI in TAVI) for PVL is negligible. At LHCH we have treated 2 patients with an occluder device, and 0 patients with a repeat TAVI in TAVI, remote from the index procedure. In the UK TAVI trial, the rate of re-intervention at 12 months was 2.2% for TAVI versus 2.9% for SAVR. These data are UK-based, and more contemporary than data which appears to derive from Partner 2.	Thank you for your comment. Baseline outcomes have now been revised to reflect UK data using the last NICOR audit of the UK TAVI Registry. The UK TAVI trial is, still unpublished so their findings were not included in the analysis. The rate of re-intervention estimated by the model in the first year for surgery is 1.6% which was used to calculate the rate in the TAVI arm using a relative treatment effect calculated through a meta-analysis of PARTNER 2, PARTNER 3 and Evolut trials. The rate does not seem to overestimate reintervention in

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the UK as, the UK TAVI trial for instance, found a reintervention rate of 2.9% in the first year in the surgical cohort. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Economic report	general	general	It would appear from the accompanying text that the principle drive in restricting TAVI to those in whom surgery is unsuitable (which is stated in the introduction, Page 6, Line 4 as being inoperable or high risk), is the outcome of the economic model. The construction of the model appears to be seriously flawed. As outlined above, outcomes are derived from historic trials, not reflective of current UK practice. It is suprising that data from more recent trials were not included for the purposes of the economic modelling. In fact, the UK	Thank you for your comment. Recent trials - Leon 2021 (PARTNER 3) and Popma 2019 (Evolut) - have been added to the meta-analysis used to inform treatment effects. Moreover, in the base case scenario, only recent trials on 2nd and 3rd generation valves will be used. Publicly available NICOR

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				TAVI database provides contemporary data on outcomes specific to UK practice, and we recommend that these are considered by NICE. Modelling outcome on a lifetime QALYs, taking a 30year horizon, when the mean age in the UK is 81 (LHCH is 83), is clearly inappropriate. We note there is no data that compares TAVI and surgery after 5years and so all outcomes are predicted over the 30 year timeframe. Exacerbating this effect, is the method examining predicted outcomes over the lifetime horizon that are remote from the initial procedure eg dialysis or CVA. It is difficult to attribute such outcomes occurring more than one year after intervention to the procedure (TAVI or SAVR) itself?	audit on TAVI was used for baseline intervention outcomes. Given that the 2 interventions and their related complications are expected to affect people in the longer term, a time horizon of 15 years was used in the base case. Nevertheless, following a discussion with the committee, two sensitivity analyses using two different time horizons (5 and 10 years) were added to account for the uncertainty of extrapolating outcomes in the longer-term. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Evidence Review 8	General	general	The Evidence Review for TAVI and surgical aortic valve replacement (SAVR) included 8 randomised controlled trials which compared TAVI. Both the inclusion and exclusion of specific studies, in comparing surgical AVR and TAVI, is flawed. Giving equal weighting to trials involving largely historical practice is particularly problematic when considering outcomes which then feed into an economic analysis. For example STACATTO, which is an entirely transapical approach, which now accounts for <2% of UK practice should be excluded from clinical and economic analysis; Partner 1 which is not reflective of contemporary UK practice (3 day critical care stay, 8 day LOS, vascular injury in >10% compared to 0 crit care stay, 2-3 days LOS, vascular injury 2.5%, UK TAVI Trial/NICOR audit), and used a device that has been obsolete for >7years; the decision to exclude the UK TAVI Trial (abstract published, data presented), and several meta-analyses that have informed international guidance. Specifically, we are concerned that there are important outcome aspects that have been used to determine both safety and efficacy, as well as inform the economic model, that are simply out dated, and not a true representation of NHS practice. The draft proposal evidence review states: - a TAVI conscious sedation rate ranging 18.3%-65.1% whereas the UK TAVI audit data (2019-20) demonstrates 90.7% - TAVI ICU LOS median 2-3 days, compared to 0 days - Total TAVI IP LOS between 3 and 9 days vs 3 days - TAVI 30/7 Mortality ranging from 0.4% in the low risk Partner 3 trial to 5.9% in Staccato vs 1.3%	Thank you for your comment. The STACCATO trial has now been removed from the economic model based on the transapical access route not being in line with current practice. However, this trial data remains included in the main analysis for the clinical review, as per the review protocol. To remove the trial would have required a post-hoc change to the protocol. The health economic analysis now uses in the base case treatment effects estimated from trials evaluation only 2nd and 3rd generations valves (PARTNER2, PARTNER3, Evolut), as they were considered to reflect better current UK practice and contemporary valves outcomes. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				- Major vascular complications between 2.2% in Partner 3 to 11% in Partner 1 vs 2.4% - CVA between 0.6% (Partner 3) and 8.8% Staccato vs 2.1% - TAVI 1yr mortality between 1% (Partner 3) and 24.2% (Partner 1) vs 4.6%. A review of the evidence regarding transfemoral only TAVI vs sAVR would have been more relevant to UK practice. Earlier trials include significant numbers of patients undergoing non femoral access, and demonstrate worse outcomes. As discussed above, in contemporary UK practice, TAVI is overwhelmingly performed via the transfemoral route and the evidence review should reflect this.	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Liverpool Heart and Chest NHS Trust	Guideline	012	003	Recommendation 1.5.3, Offer surgery, if suitable (by median sternotomy or minimally invasive 3 surgery), as first-line intervention for adults with severe aortic stenosis, 4 aortic regurgitation or mixed aortic valve disease. As highlighted above, there is no discussion regarding type of surgical AVR. This is an important distinction that is detailed in international guidelines.	Thank you for your comment. Comparison of biological and mechanical valves was not prioritised by the committee for review within the guideline.
Liverpool Heart and Chest NHS Trust	Guideline	012	006	Recommendation 1.5.4. Offer TAVI, if suitable, to adults with non-bicuspid severe aortic stenosis, *if surgery is unsuitable*. This implies the recommendation is restricted to inoperable or high risk patients – certainly the possibility of TAVI in elderly, comorbid or frail patients in whom traditional surgical risk scores might calculate an intermediate, or even low surgical risk, where surgery is suitable, is not explicitly stated. As discussed above, this would be at odds with current international guidance, which is based on published evidence that was not represented, in its entirety (eg Evolute Low risk) in the committees evidence review.	The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					evidence relevant to the review protocol is included and reviewed for interpretation. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear.
Liverpool Heart and Chest NHS Trust	Guideline	036	010	The evidence review which states 'possible harm for TAVI for mortality, need for re-intervention and hospitalisation' does not appear to stand up to scrutiny. Published meta-analyses and the meta-analysis from the committee's economic model show a strong trend for reduced mortality with TAVI.	Thank you for your comment. Evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes). Published meta-analyses that were excluded were used to identify studies relevant to this review protocol and all relevant studies were included in evidence review H.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We note also that the risk ratios or hazard ratios did not suggest large differences between the two groups for many outcomes but the committee considered any difference in mortality based on the absolute risk difference to be important. This is described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for most outcomes and the role health economic modelling had in the decision process. The health economics analysis took a different approach as we were interested to capture short-term mortality benefits as well to assess cost-effectiveness. Hence, we looked at mortality benefits at 1 and 2 years and assumed no benefit in the long-term, as found in the clinical review.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Liverpool Heart and Chest NHS Trust	Guideline	038	016	The draft consultation states that "The committee agreed that TAVI is usually reserved for when surgery is not suitable. The guidelines therefore reflect current clinical practice". This is inaccurate. Current UK practice, reflected in NICE IPG586 is a Heart Team decision, assessing surgical risk in conjunction with age, comorbidity and frailty, patient choice and anatomical considerations, and TAVI is therefore undertaken in patients of intermediate and even low surgical risk. This position is supported by an evidence base which was not considered by the committee (see below).	Thank you for your comment. We edited that statement to highlight the fact that, although offering TAVI to high risk should have a minimal impact, offering surgery to intermediate and low risk would likely lead to an important change of practice in the NHS.
Liverpool Heart and Chest NHS Trust	Guideline	general	general	General comments 1. As an Aortic Valve Heart Team we disagree with the thrust of the draft recommendation that all patients with severe AS should be offered surgery as first line, with TAVI being considered only where surgery is unsuitable (high risk or inoperable patients) with non bicuspid anatomy. 2. The proposed guidance is likely to substantially reduce the numbers of eligible patients being treated effectively for severe aortic stenosis. It is not feasible that surgical units would be able to deal with the cohort of patients who would be denied TAVI, particularly as the UK enters a recovery period post COVID, and the survival of medically treated patients is poor. The monthly mortality of those on waiting lists is estimated to be in the order of 4% (Malaisrie et al, Ann Thorac Surg 2014).	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). See evidence review H for a discussion of the evidence.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				3. In common with many other UK valve centres and in line with NICE guidance (IPG586, section 1.3) we believe that an experienced MDT is most appropriate forum for decision making regarding optimal intervention for individual patients. We are surprised that the current draft recommendations make no mention of the Heart Valve Team as multidisciplinary team working is an established part of treating patients with severe cardiac disease, recognised in all major guidelines. Removing this critical aspect, or downgrading its importance, would appear to be a retrograde step. 4. Equally surprising in its omission is the importance of patient choice. It is notable that there was no patient representation on the committee. Given the age, frailty and comorbidity of the UK TAVI population (data available from the UK TAVI audit 2019-2021, and UK TAVI trial), it is astonishing that a procedure undertaken under local anaesthetic, with a median LOS of 2-3 days, and rapid recovery, would be compared unfavourably to a highly invasive surgical procedure, incorporating GA, sternotomy, a median LOS of 8 days (2 on critical care) and a much more prolonged recovery measured in months. 5. In restricting TAVI recommendations to those patients in whom surgery is considered unsuitable, the draft proposals seem to contradict international guidelines which highlight the importance of age, life expectancy, frailty, and comorbidity, as well as anatomical factors, in deciding the optimal strategy. European guidance (ESC/EACTS 2017, published prior to the low risk trials) allows TAVI a Class 1 indication for patients considered unsuitable for surgery, and those aged >75 at high and	NICE and NHSEI have published a joint implementation strategy alongside the guideline. All the advantages of TAVI compared to surgery were accounted in the model: the shorter hospital LOS and ICU, the lower cost of rehabilitation and the higher quality of life during the first year after the procedure due to complications and recovery. Still, TAVI remains a very expensive procedure mostly due to the high price of the device itself. As the model shows, lower prices would make the technology very convenient for the NHS but until this is achieved, TAVI remains non cost effective for people at low or intermediate surgical risk. Patient choice is given when there are equally cost effective treatment options. Thank you for your comment. The clinical and cost effectiveness of

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intermediate surgical risk. The 2020 ACC/AHA guidelines give a Class 1 indication for TAVI, specifically recommending that trans-femoral TAVI is preferred to surgery in patients aged over 80, or younger with a life-expectancy of 10 years or less. In patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery is recommended based on shared decision-making. These guidelines recognize TAVI as a safe and effective procedure for treatment of severe symptomatic AS in all adults regardless of estimated surgical risk, and that decision-making should be individualized based on patient-specific factors such as longevity, comorbidity and frailty. Both of these international guidelines are in line with contemporary practice in the UK whereas the proposed NICE guidance appears to be a backward step. The BCS/STCS/BCIS Joint Statement on Clinical Selection for TAVI (2017), most relevant to UK practice, recommends discussion at Heart Team MDT, and allows TAVI for patients at intermediate surgical risk in whom other risk factors make TAVI preferable to SAVR. We note that contemporary SCTS/NICOR UK data would suggest that the mortality following isolated aortic valve surgery in all age groups is low, across all risk groups, particularly those in the low and medium risk categories:	MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. There were two lay members on the guideline committee with equal status to all the other members. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Table 20: *In Hospital Mortality rates (%) following isolated AVR in the UK by age category (years) for the past 3 years*	No distinction is made between different surgical valve types as this subgrouping strategy did not explain any heterogeneity that was found in the meta-analyses and no recommendations could therefore be made by the committee regarding biological and mechanical valves

Nation	Age group, 2016-19 (aggregate data)		
	<75	75-80	>80
UK	0.9	1.3	1.2
England	0.8	1.3	1.3
Northern Ireland	0.5	0.9	0.0
Scotland	1.7	0.5	1.1
Wales	1.1	2.7	0.0

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Table 23: *In Hospital Mortality rates (%) following isolated AVR in the UK by predicted operative risk category (Low, Medium, High – by EuroSCORE 2) for the past 3 years*	

Nation	Age group, 2016-19 (aggregate data)		
	Low risk (<4%)	Medium risk (4% - 8%)	High risk (>8%)
UK	0.7	2.2	6.1
England	0.7	2.3	5.6
Northern Ireland	0.4	0	25
Scotland	1.4	1.7	0
Wales	0.6	2.0	15

Total case numbers are small in the High Risk category outside England. For numbers see Table 22.

When considering the optimal treatment strategy in such patients however, we recognise that a more minimally invasive approach, such as TF TAVI, offers gains related to reduced critical care resource and LOS, and from a patient perspective far shorter recovery times, and the possibility of retaining a higher functional status.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				6. We note in the draft proposals that no distinction is drawn between mechanical and bioprosthetic valves for those patients in whom surgery is recommended, an issue that is given prominence in both international guidelines. In addition prominence is given to minimally invasive aortic valve surgery despite two UK RCT's which failed to show superiority of this technique. 7. With regards to the post COVID era, it must be recognised that TAVR has significant advantage over SAVR, reflecting a median ITU bed stay of 0 days, and a shorter overall hospital stay. Our own LHCH audit data mirrors the NICOR/BCIS national audit data – median hospital stay is 3 days with no critical care requirement. At a time when the burden on healthcare resources is huge, and there will be a necessary push to clear an enormous backlog, the use of minimally invasive transfemoral TAVI would seem advantageous. Coupled with the recognition that severe AS has a mortality on surgical waiting list of approx 4% per month (Malaisrie et al,Ann Thorac Surg 2014), there is an imperative to treat patients with severe AS in a timely and efficient manner. UK data would suggest that there was a significant reduction in surgical intervention for aortic valve disease (73%) during March-May 2020, compared to a decrease in TAVI procedures of 11%. In comparison to pre-COVID period those undergoing both SAVR and TAVR were younger (Mohamed et al, Eur Heart J Qual Care Clin Outcomes. 2020 Oct 20). We draw attention to the NHS England and NHS Improvement endorsed guidance for the management of	

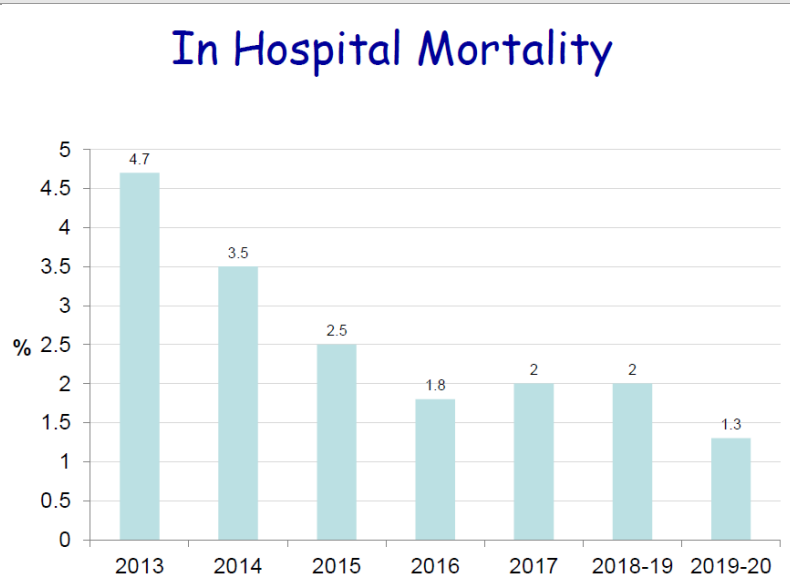
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cardiology patients during the COVID pandemic, supported in the UK by (BCS/BCIS). These guidelines suggested that providers considered the use of minimally invasive transfemoral TAVI as an alternative to aortic valve surgery for intermediate and low-risk patients in order to reap the benefits of reduced ITU resource allocation and early discharge. 8. As the document suggest, 80% of surgical AVR is undertaken in low risk, often younger patients. SCTS audit data suggest a mean age of 63. The BCIS UK TAVI data show a 20-30% annual increase in TAVI procedure numbers, from 66 in 2007, to 781 in 2010, 2516 in 2015, and 6076 in 2019-20, yet the mean age of the patients remains 81. Our local Trust audit demonstrates a mean age of 83. Thus in the UK, TAVI is undertaken in an older cohort, and as currently practised by MDT decision, may include elderly patients of high, intermediate or even low surgical risk. It is unlikely that these patients would be offered surgery as an alternative to TAVI. The much more likely outcome of the draft recommendations is that such patients will be offered medical therapy with the attendant costs of repeat hospitalisations. 9. The lack of any reference to cardiac rehabilitation is also disappointing. This guidance would have provided opportunity to strengthen recommendations around the rehabilitation offering to both surgical, or percutaneously treated, heart valve disease patients.	
Manchester University NHS	Economic report	007	001	**Model utilised** TAVI group older, more previous cardiac surgery, more coronary interventions, and higher logistic EuroSCORE, which means a propensity	Thank you for your comment. The committee decided to limit the clinical search to randomized

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation Trust				score match would be more appropriate to compare the costs as opposed to the skewed model utilised.	controlled trials and not include other types of evidence, such as propensity score match analyses (see appendix A evidence review /h for the review protocol). Likewise, the model was built only on randomized studies as recommended in the NICE manual as these often represent evidence with a lower risk of bias. Though, given the recent technological improvement of TAVI valves, we are limiting the studies including in the meta-analysis to trials assessing 2nd and 3rd generation valves only: PARTNER 2 PARTNER 3 Evolut
Manchester University NHS Foundation Trust	Economic report	015	-	**Mortality 30 days risk ratio 0.88** BCIS mortality data 1.3% SCTS mortality data 2.7% Which means the ratio is 1.3/2.7 = 0.48 BUT TAVI group older, more previous cardiac surgery, more coronary interventions, and higher logistic EuroSCORE	Thank you for your comment. The percentage 2.7% is the mortality of intermediate-risk patients receiving surgery, which represents only a small part of all the patients undertaking an AVR in the UK as the majority of surgical procedures are performed on low-risk patients (88% according to the latest NACSA audit). The actual

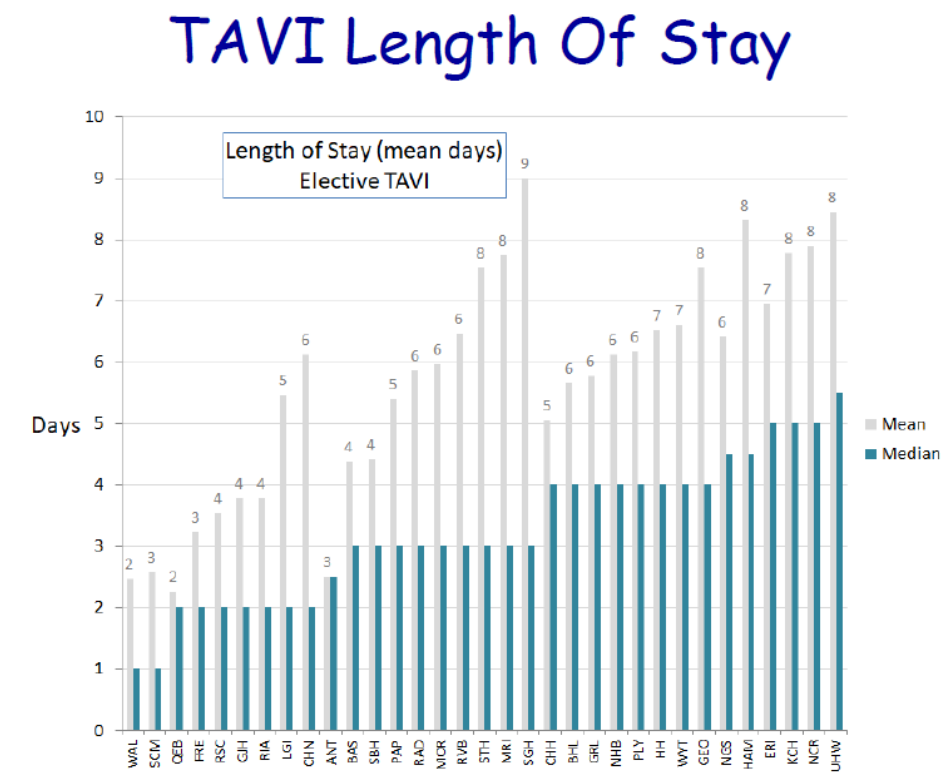
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 BCIS TAVI DATA	weighted average mortality of SAVR across all the risk groups is 0.95%, so even lower than the mortality reported in BCIS. Of course, as you mentioned, TAVI cohort is older and has a higher mean STS and EuroSCORE and therefore a comparison between these 2 percentages would be of little help. This is the reason treatment effects in the model come exclusively from randomized controlled trials where the pre-procedural randomisation ensures that patients in both arms are comparable, and therefore, that the relative treatment effect estimated is correct.
Manchester University NHS Foundation Trust	Economic report	016 - 017	-	**Intermediate risk £9,658 NHS Reference Costs 2017-2018, High risk £11,979** The staff, equipment and resources are identical, so this is a fictitious difference.	Thank you for your comment. The committee agreed to use the same HRG EY21B for all risk to estimate the cost of a TAVI intervention, which therefore does not vary anymore according to the risk.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Manchester University NHS Foundation Trust	Economic report	027	010	**Hospitalisation £2,010 vs £1,575** As all surgical cases go to ITU post procedure, and <5% of TAVI cases do so, the surgical cases incur at least a £1,415/night in ITU charge over the TAVI cases. BCIS National Audit Adult Interventional Procedures 1st April 2019 to 31st March 2020 data demonstrates a median stay of 2.5 - 3 days. Surgical isolated AVR is associated with a median length of stay of 8 days, and 9 days if combined with CABG (approx. 60% of cases). (National Cardiac Surgery Activity and Outcomes Report 2002 – 2016). Audit data in Manchester shows more than 50% of TAVIs are discharged the following day. There is also increasing national interest in daycase TAVI.	Thank you for your comment. We are currently using UK TAVI trial to inform ITU and hospital LOS in TAVI and surgical patients. The trial suggests that, in line with BCIS data, TAVI patients spend a median of 0 days in ICU and 3 days in the hospital wards, whereas SAVR patients spend 1 day in ICU and 8 in surgical ward. These data reflect low-risk patients so they were scaled up using a published source for the intermediate and high risk groups.

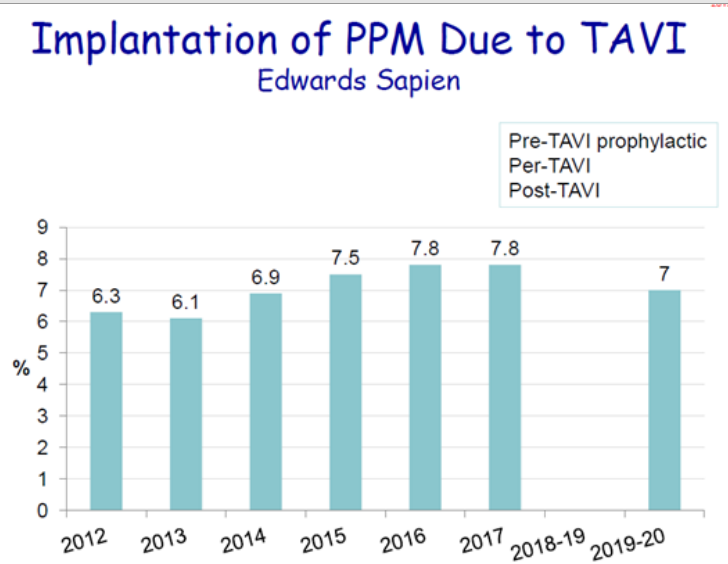
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 BCIS TAVI DATA	

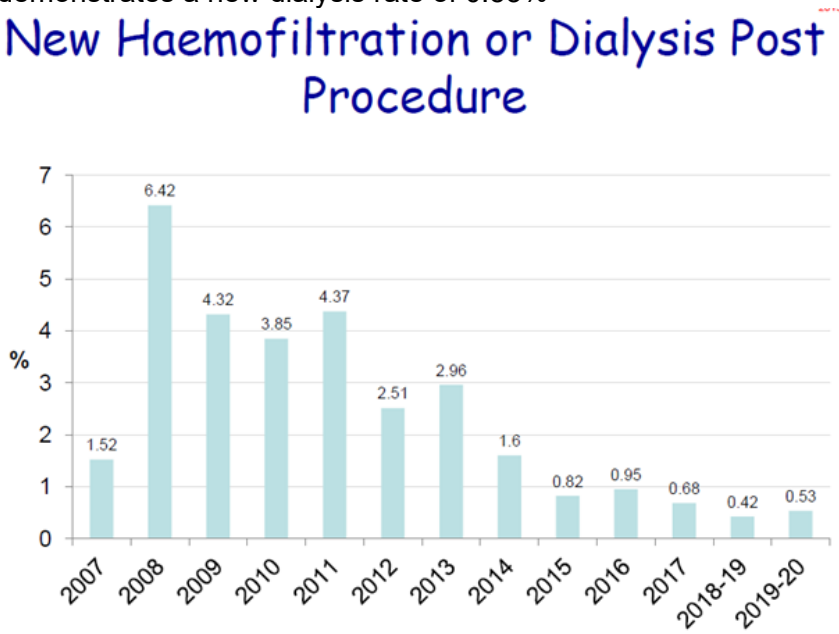
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In addition the references utilised are out of date compared to the BCIS data. (Leon 2016 ref 12 & Smith 2011 ref 32) The use of codes XC01Z, XC02Z, XC03Z, and XC04Z indicate that multiorgan failure post cardiac surgery, which is much more common than after TAVI is financially rewarded in the risk model.	
Manchester University NHS Foundation Trust	Economic report	043	005	**Pacemaker implantation £402 vs £164** This figure doesn't reconcile with BCIS National Audit Adult Interventional Procedures 1st April 2019 to 31st March 2020 data that demonstrates a pacemaker rate post TAVI of 7%, which at a price point of £1,000/pacemaker equates to £70/patient.	Thank you for your comment. The current rate used in the model for pacemaker implantation is 9% and comes directly from the last NICOR audit of the UK TAVI registry.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 BCIS TAVI DATA The introduction of the cusp overlap technique, which is currently widely used has a pacemaker rate of 3 - 5.5%, which at a price point of £1,000/pacemaker equates to £30 - 55/patient. (JACC Cardiovasc Interv. 2019 Sep 23;12(18):1796-1807. & Circulation: Cardiovascular Interventions. 2021;14:e010330) Furthermore the use of incorrect pacemaker rate to influence long term survival invalidates the whole analysis – p15	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Manchester University NHS Foundation Trust	Economic report	043	005	**Dialysis data £1,621 vs £2,810** Local data from Manchester Royal infirmary (N>700 TAVI cases), less than 1% of patients needed dialysis post TAVI who did not have it prior to the procedure. This is in accordance with national BCIS data below. This NICE data doesn't reconcile with BCIS National Audit Adult Interventional Procedures 1st April 2019 to 31st March 2020 data that demonstrates a new dialysis rate of 0.53%  BCIS TAVI DATA	Thank you for your comment. The baseline risk for dialysis was taken from an analysis by Ferro and colleagues on dialysis occurring after a TAVI intervention using UK TAVI trial. This source was preferred as the authors conducted an analysis on mortality at 30 days and in the longer term that was used in the model to calculate how many of those were alive at 30 days and after 1 year. The resulting rate was 1.5%. We could not find dialysis rate in the latest published version of BCIS audit. Charles J. Ferro, Jonathan P. Law, Sagar N. Doshi, Mark de Belder, Neil Moat, Mamas Mamas, David Hildick-Smith, Peter Ludman, Jonathan N. Townend, Dialysis Following Transcatheter Aortic Valve Replacement: Risk Factors and Outcomes: An Analysis From the UK TAVI (Transcatheter Aortic Valve Implantation) Registry,

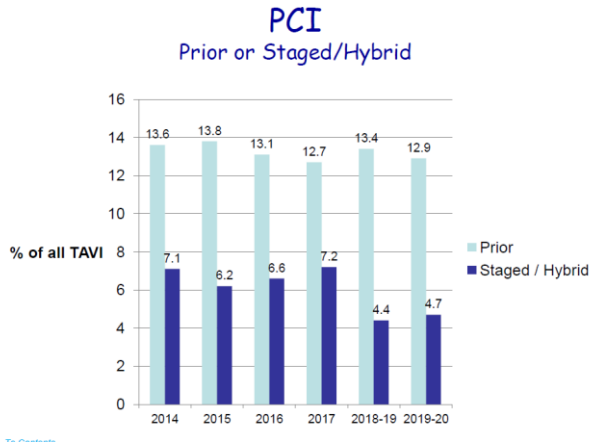
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					JACC: Cardiovascular Interventions, Volume 10, Issue 20, 2017, Pages 2040-2047, ISSN 1936-8798, https://doi.org/10.1016/j.jcin.2017.05.020.
Manchester University NHS Foundation Trust	Economic report	043	005	**Echo £377 vs £109** Surgical AVR utilises transoesophageal echocardiography, as opposed to trans thoracic echocardiography. This makes the figures supplied by NICE unlikely to be accurate, as the probe, covering, TOE accredited technician, and machine are all more expensive for surgery. The same pre and post procedure transthoracic echo surveillance is utilised. This ignores the often echo ? tamponade post cardiac surgery, which is negative, that is rare post TAVI.	Thank you for your comment. The committee agreed that people with paravalvular leak would undergo an echocardiography a year and that the cost of the procedure would be similar for a surgery or a TAVI patient. Although TOE during surgical AVR has become common practice in the last decade, it is done by the anaesthetist as part of the anaesthetic monitoring of patients so it doesn't require any extra resource. All the extra costs of surgery are expected to be included in the NHS Reference Costs HRG, which is why a surgery procedure is more expensive than

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI if we do not take into account valve costs.
Manchester University NHS Foundation Trust	Economic report	043	005	**No invasive coronary angiogram costs in TAVI group - not factored in** Elderly have gated CT scans for TAVI assessment, which allows coronary artery assessment at the same time, saving on the cost of coronary angiography (coronary angiography rate pre TAVI 25%, coronary angiography rate pre sAVR 100%). Elderly surgical patients usually have CT scans to assess for ascending aortic calcification, and always have coronary angiography. So, the cost of more coronary angiograms in the surgery arm needs to be included.	Thank you for your comment. As per the guideline scope, we did not look into the evidence related to coronary artery disease in patients with heart valve disease and into the appropriateness or not to leave coronary disease unaddressed, particularly given the difficulties with coronary access for percutaneous coronary intervention in patients developing angina symptoms and acute coronary syndromes later in life. The recommendations refer to valve disease only, and not to revascularisation or revascularisation disease management
Manchester University NHS Foundation Trust	Economic report TAVI	025	029	**Surgical AVR and Combined AVR + CABG** BCIS National Audit Adult Interventional Procedures 1st April 2019 to 31st March 2020 data indicates that 12.9% - 17.6% of patients undergoing TAVI also have a PCI. This makes 12.9% -17.6% of TAVI patients comparable to valve and graft patients undergoing surgery, and not isolated AVR as in the model. In reality at least 60% of patients undergoing surgical AVR require	Thank you for your comment. The committee agreed that the right comparator for TAVI is isolated AVR. Although there is outcome data for surgical AVR plus CABG, there is no outcome data for TAVI plus PCI.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				CABG at the same time as the threshold for revascularisation in cardiac surgery is much lower (related to putting the patient on cardiopulmonary bypass).  BCIS TAVI DATA Valve and graft surgery patients have higher mortality 5.4 vs 2.7%, longer length of stay 9 vs 8 days, and attract a higher tariff EA17Z verses EA20Z, than isolated AVR surgical cases. (National Cardiac Surgery Activity and Outcomes Report 2002 – 2016) Using the wrong surgical model to compare TAVI against invalidates the whole analysis.	The trials used to estimate the treatment effects all compared TAVI vs isolated AVR, hence it is not possible to apply these findings to a different kind of intervention such as AVR + CABG. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Manchester University NHS Foundation Trust	Evidence Review H	133	014	**Reintervention rates after TAVI** The re-intervention rate following TAVI is extremely low using accurate CT valve sizing and current valve prostheses that minimise paravalular leak. The re-intervention quoted by NICE is completely out of date and the assumption that re-intervention is repeat TAVI is incorrect (the data included in the NICE economic analysis refers to re-intervention for paravalvular leak using vascular plugs not repeat TAVI). The TAVI re-intervention rate in Manchester over the last 7 years is 1/700 cases ie 0.1% - several orders of magnitude different to the approximately 10% used in the NICE economic analysis. Conversely, registry data suggests that approximately 10% of TAVIs are performed in patients with previous surgical bioprostheses. The TAVI intervention rate post TAVI is therefore approximately 0.1%, at 5 years (10 year data limited but likely to be low), whereas the TAVI rate post surgical AVR is significant and likely at least is 5-10% at 10 years (exact figures not known). The reason for this difference is that surgical valves are sometimes much smaller than TAVI valves (due to need to accommodate the sewing ring in patients with small annulus size) and may in these patients re-narrow much quicker as a result (so-called patient prosthesis mismatch). The low re-intervention rate post TAVI also reflects the means age of >80 years and the more limited life expectancy.	Thank you for your comment. The need for re-intervention outcome in the clinical review does not refer solely to repeat TAVI and includes data as defined for each study. In the revised version of the model, reintervention risk ratio is calculated using studies on 2nd and 3rd generation valves. A scenario analysis where this figure is calculated from the Evolut and PARTNER 3 only was conducted as well. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Manchester University NHS Foundation Trust	Guideline	?	?	**MDT** No mention of MDT work in guideline All patients should be discussed at an MDT where a TAVI operator, interventional cardiologist, cardiac surgeon, vascular radiologist and echocardiographer are present. Decision should be made taking into account patient preferences following a full discussion of options with the patients (GMC guidance concerning consent). The reality is that surgeons do not want to operate on either intermediate or high risk patients and many elderly patients will refuse to have surgery. If the guidance recommends surgery in these patients, against consensus opinion, discussions and decision making will be made much more complex. This will result in a large number of additional investigations, addition clinic appointments and additional MDT discussions with the same decision made in the end. This will significantly add both cost and significantly delay intervention. Delays are already too long with deaths on waiting lists (https://www.valveforlife.co.uk/uk-valve-data, https://7e2bc30e-7afe-44ce-a29f-767eb1392a95.filesusr.com/ugd/8f9091_8a2cc83971104341ae3d25cfeead8531.pdf), leading to several media reports in the past in this patient group eg https://www.bbc.co.uk/news/uk-wales-27673665 , the patients who died in these reports were patients with severe aortic stenosis awaiting surgery).	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Discussions with patients will also be difficult as many patients will request TAVI. A related issue is that patientS undergoing conventional surgery are not routinely discussed in an MDT – this could lead to idiosyncratic decision making. Many patients without full MDT review may be offered surgery on the basis of an echocardiogram performed by a physiologist without confirmation from an imaging cardiologist and MDT of the severity of aortic stenosis (which is complex and specialised), this could result in a significant number of unnecessary surgical operations. All patients considered for intervention with severe aortic stenosis should be discussed in a full MDT as detailed above.	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Manchester University NHS Foundation Trust	Guideline	012	003 - 005	The impact of COVID in Manchester has been that with ITU filled with COVID patients very little cardiac surgery has been done. In contrast TAVI procedures have continued with no TAVI waiting list currently. This means that the wait for surgical AVR is substantial with >150 patients awaiting cardiac surgery. This means that any shift from TAVI to sAVR will lead to substantial treatment delays and consequently mortalities on the waiting list would be a likely risk, at least in the short to medium term.	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Manchester University NHS Foundation Trust	Guideline	012	003 - 005	Social care / rehabilitation costs in the surgery arm may be significantly underestimated and could have a major effect. The Baron Partner 2 paper (https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.118.035236) estimated this as an excess of $10000 per sAVR making TAVI cheaper overall - the NICE document calculates one tenth of this ie £950. NICE quotes ref 16 Mack (Partner 3) - but from what I can see this has no data on social care costs Data from Liverpool in 2005 (preTAVI) shows 24% of over 79 years patients having sAVR went to a nursing home. US data (Long-Term Fate of Patients Discharged to Extended Care Facilities After Cardiovascular Surgery - Ann Thorac Surg 2013;96:871–8.) suggests similar rates with 90 day average nursing home stay. Cost would be approx. £10,000 for 90 day stay, equating to £2.500 per sAVR patient if intermediate and high risk patients are treated with sAVR. The rate of nursing home discharge post TAVI in elective patients coming from there own home in Manchester is <1%.	Thank you for your comment. It is often challenging to compare NHS costs with US costs as the latter are often inflated due to the nature of the American health care system. Moreover, Baron estimated rehabilitation costs based on Medicare claim, which is known to be a not very reliably methodology. In the NICE model, we counted people requiring home-based physiotherapy and intermediate care centre case, and then we calculated the costs based on the actual resource usage observed in the trial. We believe this methodology offers a more precise estimation of post-admission costs.
Manchester University NHS Foundation Trust	Guideline	012	003 - 005	Potential cost containment : in our view the tariff for TAVI is outdated and too high (reflects outdated hospital costs) and the prosthesis cost is also too high (it should come down now all the pivotal trials have been done). TAVI should be the preferred option for all patients over 80 years due to prolonged recuperation periods post surgery in these patients (many of whom are low risk of death according to STS score but have long hospital stays and long post discharge recuperation periods) and those with	Thank you for your comment. The methodology to calculate cost of TAVI has been updated to reflect current costs of the intervention and of the valve. The intervention cost now is in line with the figure reported by

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				significant co-morbidities (high surgical risk) below this age. All patients for AVR (surgery and TAVI) should be discussed in an MDT. Efforts should be made to identify severe AS prior to decompensation (development of heart failure in most cases) as hospital admission in these patients is lengthy and very expensive with a high rate of adverse events.	several Trusts (£5,500) and the cost of the valve comes directly from the NHS Supply Chain. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. A recommendation based on age could not be made as the analysis could not be stratified by age due to the guidance set out in NICE's social value judgements paper https://www.nice.org.uk/about/who-we-are/our-principles

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Manchester University NHS Foundation Trust	Guideline	012	003	**Surgery – MIS first-line treatment (minimally invasive surgery)** We are unaware that any evidence exists with regard to recommending MIS as an equal treatment to conventional surgery or as advantageous to TAVI. The cost of sutureless valves used in MIS is significantly higher than conventional surgical valves. This treatment cannot be recommended in the absence of economic considerations and randomised comparisons with conventional surgery and TAVI.	Thank you for your comment. Regarding the equal weighting given to minimally invasive and standard surgery, the rationale for this is outlined in the committee discussion section of review H. Despite some clinically important harms of minimally invasive surgery being identified across the included studies, and a health economic study that suggested minimally invasive surgery was not cost-effective compared with median sternotomy replacement, it was noted that all RCTs were small and for many outcomes only a small number of events were observed. The health economic study was also limited for the same reasons, as it was based on one of the RCTs included in the clinical evidence. It was also limited to a 12 month time-horizon, which may be too short to draw conclusions about cost effectiveness over a lifetime, though the committee agreed

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					it is likely there would not be a large difference in outcomes after 12 months. The committee agreed that the evidence included was insufficient to limit the use of minimally invasive surgery and a decision was made to offer either in those undergoing surgical replacement of the aortic valve, with the decision to be based on patient characteristics and preferences. As minimally invasive surgery is not suitable for most patients it was not prioritised as a research recommendation.
Medtronic Limited				**Medtronic challenge if 'clinical review' reflects best practice and suggests the guidance references 'surveillance in a specialist valve clinic'.** The BHVS *Network Based Care for Heart Valve Disease* (2020) stipulates that 'care is best delivered by healthcare professionals with appropriate competencies, ideally in a heart valve clinic.' Chambers et al (2013) demonstrate that referral to valve clinics 'improves adherence to international guidelines and reduces unnecessary echocardiograms.' Chambers and Lancellotti (2019) also underline valve clinics critical role in determining the correct timing of intervention.	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Chambers JB, Ray S, Prendergast B, et al. Specialist valve clinics: recommendations from the British Heart Valve Society working group on improving quality in the delivery of care for patients with heart valve disease. Heart 2013;99:1714-1716. • https://www.bhvs.org.uk/bhvs-blueprint/ • Chambers JB, Lancellotti P. Heart Valve Clinics, Centers, and Networks. Cardiol Clin. 2020 Feb;38(1):65-74. doi: 10.1016/j.ccl.2019.09.006. Epub 2019 Nov 1. PMID: 31753178.	
Medtronic Limited				**Medtronic feel that NICE should assess sutureless/ rapid-deployment valves as a stand-alone technology and not under the procedural banner of minimally invasive cardiac surgery.** Medtronic would like to share some concerns with the Committee regarding sutureless valves which are used in surgical aortic valve replacement by full/median sternotomy and minimally invasive surgery. Recent results from the PERSIST-AVR randomised controlled trial failed to demonstrate superiority of sutureless valves over stented valves. Non-inferiority was demonstrated on the primary composite MACCE (major adverse cerebral and cardiovascular events) outcome at 1 year. However, nominal values were slightly higher in the sutureless group (8.1% of patients in the sutureless group; 7.8% of patients in the stented group). No benefit has been observed on either short term or long-term mortality with nominal values being again slightly higher for sutureless valves at 1 year (3.7% of patients in the sutureless group; 3.4% of patients in the stented group). These findings are consistent with the results of the CADENCE-	Thank you for your comment. The protocol for this review (appendix A evidence review H) did not stratify the data to enable the committee to evaluate the evidence for sutureless valves separately. The committee made this decision because they agreed that there was no clinical rationale for the effectiveness of sutureless valve to differ from other interventions. Furthermore, there was no heterogeneity found in the meta-analyses which supports the pooling of studies. There was evidence from one small study that used sutureless valves (n=97), with low events rates reported (e.g. 2 vs 0 pacemaker implantations in MI vs surg groups at

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				MIS randomized controlled trial in which 30-day mortality was reported to be nominally higher for minimally invasive rapid deployment aortic valve replacement (MIS-RDAVR) as compared to full-sternotomy conventional aortic valve replacement (FS-AVR) (4.3% of patients in the MIS-RDAVR group; 2.1%% of patients in the FS-AVR group). Medtronic would like to also draw to the attention of the Committee that sutureless valves have been reported to be associated with statistically significant higher rates of pacemaker implant. In the PERSIST-AVR trial, pacemaker implant at 1 year was reported in 11.1% of patients in the sutureless group and in 3.6% of patients in the stented group (-7.4; 95% credible interval (-10.9 to -3.8)). We would also like the committee to note that sutureless aortic heart valves/ rapid deployment aortic heart valve replacement were listed in the 2020/21 National Tariff Payment System High-Cost Tariff Excluded Devices (HCTED) and are again listed for 2021/22 National Payment System. https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/ Medtronic are surprised that sutureless/rapid-deployment valves appear to have been included within the recommendation for "minimally invasive cardiac surgery" despite the lack of supportive clinical data and substantial incremental costs associated with the technology vs standard SAVR valves.	30 days). This would not have been sufficient evidence to make a separate recommendation because of the uncertainty in the true effect estimate and because there could be other factors causing the difference in effect between this study and the others (one study isn't sufficient to consider a subgroup effect). Data from the PERSIST-AVR trial was not included as it compared perceval sutureless bioprosthesis with a conventional sutured stented bioprosthesis and therefore did not meet the review protocol criteria. CADENCE-MIS was not included because it compared minimally invasive surgery rapid-deployment aortic valve replacement (AVR) with those of conventional full sternotomy AVR and did not meet the review protocol crtieria (see appendix A evidence review H).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Medtronic believe that all technologies should be assessed with the same rigor and therefore recommend that sutureless valves are analysed in terms of their cost-effectiveness versus standard SAVR. Medtronic recommend that the committee clarifies that the multidisciplinary heart team needs to discuss the type of access for the patient's intervention (median sternotomy, minimally invasive or transcatheter) and the choice of valve. Minimally invasive surgery can be done with many different valves, not necessarily sutureless valves, for which the evidence is limited. **REFERENCES:** • Fischlein T, Folliguet T, Meuris B, Shrestha ML, Roselli EE, McGlothlin A, Kappert U, Pfeiffer S, Corbi P, Lorusso R; Perceval Sutureless Implant Versus Standard-Aortic Valve Replacement Investigators. Sutureless versus conventional bioprostheses for aortic valve replacement in severe symptomatic aortic valve stenosis. J Thorac Cardiovasc Surg. 2021 Mar;161(3):920-932. • Borger MA, Moustafine V, Conradi L, Knosalla C, Richter M, Merk DR, Doenst T, Hammerschmidt R, Treede H, Dohmen P, Strauch JT. A randomized multicenter trial of minimally invasive rapid deployment versus conventional full sternotomy aortic valve replacement. Ann Thorac Surg. 2015 Jan;99(1):17-25.	
Medtronic Limited	2	Covid-19 response		It is well documented that the COVID-19 pandemic has had a dramatic burden on healthcare resources across the NHS and has impacted timely access for patients with cardiovascular diseases as described by Einstein (2021) In response to the pandemic, NHS England and NHS Improvement provided guidance for the management of cardiology patients. This	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				guidance was supported in the UK by national societies (BCS/BCIS). Similarly, in European societies (ESC) together with Spanish society (ACI-SEC) adapted their recommendations on the management of cardiovascular diseases, including Severe Symptomatic Aortic Stenosis (sSAS). These adapted guidelines recommend that, where possible, providers are to consider the use of minimally invasive transfemoral TAVI as an alternative to surgery for intermediate and low-risk patients. These recommendations are based upon several factors, including: · TAVI is an opportunity to optimize the hospital resource utilization - avoids general anesthesia and intubation, reduces/prevents ICU stay, accelerates recovery and hospital discharge. · Foster adequate patients' prioritization · Address patient preferences · Maintain the highest standard of care for urgent cases like COVID-19 patients. Further work carried out in the UK, Khialani and MacCarthy (2020) on severe aortic stenosis during the COVID-19 pandemic provided supportive evidence that early discharge from hospital is safe. We therefore respectfully ask to the committee to take account of these recommendations put forward from the clinical societies when finalising the guideline for publication.	an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account. NICE guidelines do not typically take into consideration recommendations from other guidelines. We conduct our own evidence review which is often more systematic and includes cost as well as clinical effectiveness. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				REFERENCES: • Einstein et al. International Impact of COVID-19 on the Diagnosis of Heart Disease. Journal Of The American College Of Cardiology 2021; 77(2): 173 – 85. • ESC Position June 2020: The collateral damage of COVID-19: cardiovascular disease, the next pandemic wave. Available at: https://www.escardio.org/The-ESC/Advocacy/Shaping-policy-and-regulation/ESC-positions/the-collateral-damage-of-covid-19-cardiovascular-disease-the-next-pandemic-wav#.Xtk73uKIZI4.linkedin • Adamo et al. Patient with heart failure: importance to treat valvular diseases. European Heart Journal Supplements 2020; 22 (Supplement P):P38–P41 • Moreno et al. Transcatheter aortic valve implantation during the current COVID-19 pandemic. Recommendations from the ACI-SEC. REC Interv Cardiol. 2020;2:230-231 • Curzen N. An Extended Statement by the British Cardiovascular Intervention Society President regarding the COVID-19 pandemic. Interventional Cardiology Review 2020;15:e01. DOI: https://doi.org/10.15420/icr.2020.10 • BCS/BCIS. Cardiology services during the covid-19 pandemic. 23 March 2020. Available at: https://www.bcis.org.uk/news/cardiology-services-during-the-covid-19-pandemic/ • NHS England and NHS Improvement. Clinical guide for the management of cardiology patients during the coronavirus pandemic. 20 March 2020. Available at: https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-guide-cardiolgy-coronavirus.pdf	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Khialani, B. and MacCarthy, P. (2020) 'Transcatheter management of severe aortic stenosis during the COVID-19 pandemic', Heart. BMJ Publishing Group, 106(15), pp. 1183–1190. doi: 10.1136/heartjnl-2020-317221.	
Medtronic Limited	All	General	General	Firstly, Medtronic would like to thank NICE for the opportunity to contribute to this important consultation. Given the widespread lack of awareness, rates of missed diagnoses and absence of a standardised care pathway for patients with Heart Valve Disease in the NHS, we welcome these clinical guidelines and believe that they are timely, relevant and provide a critical opportunity to significantly improve the care provided to patients. Medtronic would also like to publicly state that we are a manufacturer of both surgical and transcatheter heart valves. We have consistently and will continue to support the approach that NICE, in all its forms takes, in the evaluation of technologies and its place in ensuring best value for the NHS and its patients. While Medtronic generally support the modelling approach, we feel that there are significant errors in the input values used. These errors result in outputs which, in their current form, are not sufficiently robust to make informed decisions. The concerns of Medtronic are detailed below in specific comments, and we politely request that NICE take into consideration all our comments before finalising these guidelines.	Thank you for your comment.
Medtronic Limited	All	General	General	Medtronic are concerned that hospital capacity, including the use of ICU has not been considered when developing these draft guidelines.	Thank you for your comment. The cost of longer hospital LOS and ICU was one of the most important aspect of the economic model providing

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

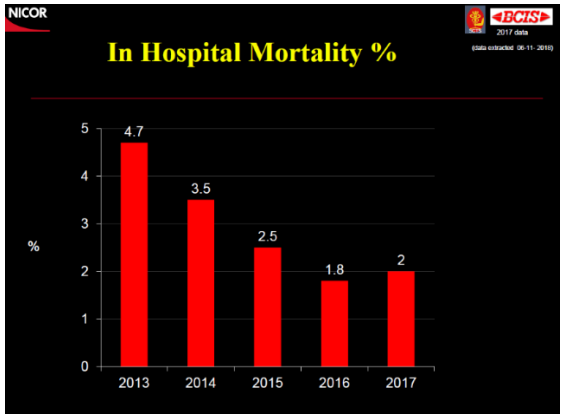
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The V-KEMS Study Group report, available at Modelling Solutions to the Impact of COVID-19 on Cardiovascular Waiting Lists Tuesday 2nd – Thursday 4th February 2021 (newton.ac.uk) stated that cumulatively over the period March to November 2020, there were an estimated 4989 patients who haven't received treatment for aortic stenosis. Of these 4989 patients it is estimated that up to 698 deaths will occur as a result of waiting for an intervention. M^{c}Calmont (2019) and Rai (2020) have provided evidence that pathway efficiencies can be achieved with TAVI procedures which can result in a same day discharge, a timeline that could never be realised with patients undergoing a SAVR procedure. As noted by Khialini and MacCarthy (2020) '***Transcatheter aortic valve implantation (TAVI) is an effective treatment for AS and has less impact on hospital (and particularly critical care) capacity than surgical AVR.'*** The backlog of cases due to the COVID-19 pandemic is well documented and aortic stenosis patients will die because of a delay in treatment. The NHS needs treatment pathways that significantly reduce hospital length of stay and free-up capacity to treat more patients. **REFERENCES:** • McCalmont, G. et al. (2019) '136 Same-day admission facilitated by a nurse led pathway reduces hospital length of stay for transfemoral transcatheter aortic valve implantation', in Heart. BMJ, p. A112.2-A112. doi: 10.1136/heartjnl-2019-bcs.133.	evidence to the recommendations on TAVI and was informed from UK sources and the UK TAVI trial in the revised version of the model. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account. The references cited did not meet the review protocol criteria (see appendix A evidence review H) which compared TAVI, standard surgery and minimally invasive surgery with each other or conservative treatment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

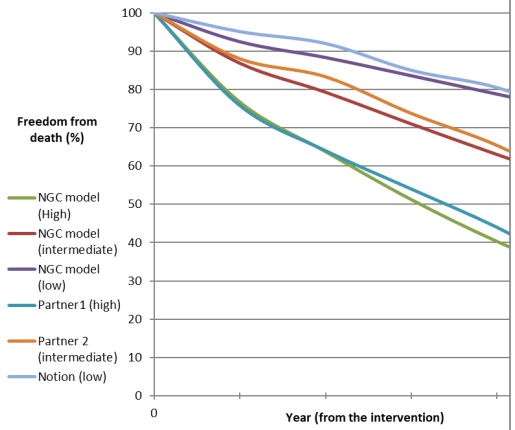
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Rai, D. et al. (2021) 'Transcatheter aortic valve replacement same-day discharge for selected patients: a case series', European Heart Journal - Case Reports. Edited by F. Giannini et al. Oxford University Press (OUP), 5(2). doi: 10.1093/ehjcr/ytaa556. • Khialani, B. and MacCarthy, P. (2020) 'Transcatheter management of severe aortic stenosis during the COVID-19 pandemic', *Heart*. BMJ Publishing Group, 106(15), pp. 1183–1190. doi: 10.1136/heartjnl-2020-317221.	
Medtronic Limited	Economic Report TAVI	042	011 - 015	Medtronic are concerned that NICE have concluded that TAVI is more cost-effective in older cohorts as these patients have a lower life expectancy and are less likely to need a second intervention. Medtronic are concerned that this statement is not consistent with the key principles of developing clinical guidelines and has the potential to discriminate against younger patients who would be otherwise offered a TAVI intervention. We therefore ask that this statement is reworded and considered under the Equality Impact Assessment.	Thank you for your comment. The committee discussed the implication of stratifying the results by age and making different recommendations in different age groups, and agreed that this was not appropriate essentially for the reasons mentioned by Medtronic. The revised model therefore is not stratifying by age anymore (only by risk) and the evidence report does not make any statement on cost-effectiveness for different age groups. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Economic Report TAVI and Economic Model TAVI	018 019 014 & 015	008 - 023 001 - 014	**The use of Martin 2017 to model survival vs General Population will underestimate the survival of severe symptomatic aortic stenosis patients at high and intermediate risk.** The survival of AVR patients versus the general population is modelled using Martin 2017 which included patients treated with TAVI between 2007 and 2014 from the UK TAVI Registry. Given the immaturity of the technology and extremely limited commissioning, it is very likely that the patients treated with TAVI in the NHS during this time were deemed inoperable with a lower life expectancy than patients suitable for surgery and therefore their survival curves are unlikely to be representative of the high and intermediate risk patients being modelled by NICE for the current assessment. This assumption is supported by the high proportion of patients with comorbidities including 80.1% having heart failure with NYHA >III and 36.73% having LVEF below 50%. As shown in the figure below, the in-hospital mortality of UK TAVI patients has dramatically improved since 2013 and this trend could likely be extrapolated back to 2007. This	Thank you for your comment. The committee looked at the descriptive statistics of Martin 2017 and give their expert opinion that this study reflects the characteristics of intermediate risk patients. The STS of 5 and logistic Euroscore of 21.9 suggest that study participants, on average, are intermediate risks. Moreover, the other characteristics reported are rather in line with the ones reported in a recent RCT on intermediate risk (PARTNER 2): • Age: 81.3 (Martin) vs 81.5 (PARTNER 2)

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				higher procedural mortality rate is clearly evident in the shape of the survival curves used in the model given the steep gradient in the first year. 15.7% of patients in Martin et al., 2017 (including 25.5% of patients between 2007 and 2010) were implanted via the transapical approach which we know is associated with higher mortality rates (Nielsen 2012, Leon 2016 and Gleason 2018 amongst others). The temporal trend toward lower TAVI mortality is evidenced even within the Martin 2017 study, where the authors compare survival in the period 2007-2010 to survival in 2011-2014 and find mortality in the early group to be higher than in the latter group. The current analysis model does not consider this evidence, but instead uses the full 2007-2014 data from Martin 2017 to inform survival. 	• NYHA class III or IV: 80% (Martin) vs 77% (PARTNER 2) • COPD: 26.2% (Martin) vs 31.8 (PARTNER 2) • Diabetes: 33.6% (Martin) vs 37.7% (PARTNER 2) In addition, LVEF between the 2 studies seems comparable as well. We are aware that mortality in TAVI patients has improved significantly during the recent years and that some approaches, such as transapical, are nowadays rarely performed because they are associated with higher mortality. Hence, it was decided to use the most recent relative survival rates provided by Martin (2011-2014) to estimate mortality in the model. The committee do not agree with the statement that patients included in the study from Martin 2017 represent inoperable or very sick patients as descriptive statistics seem to indicate they are on average intermediate risk.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It should also be considered that patients implanted with TAVI in the UK between 2007 and 2014 are very unlikely to represent the survival of patients by age group, especially for the intermediate risk model, because the patients treated with TAVI at this time will have been patients who were deemed inoperable for SAVR and therefore will have been very sick regardless of their age. **REFERENCES:** • Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. Journal of the American College of Cardiology. 2018;72(22):2687-96 • Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine. 2016;374(17):1609-20 Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. EuroIntervention. 2012; 8(3):383-389	Mortality in the high and low risk groups were estimated by applying confounders-adjusted hazard ratios recovered from the literature to the mortality in the intermediate group. The resulting survival curves for high, intermediate, and low risks reflect the survival found in trials with long follow-up (5 years, see the graph): 
Medtronic Limited	Economic			Below we have summarised our suggested revisions to the model and resultant ICERs where Medtronic feel the robustness and reliability could be improved to remove factual inaccuracies and better reflect standard	Thank you for your comment and thoughtful considerations. Most of Medtronic recommendations were

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	Model TAVI			NHS clinical practice. Please note our individual comments on each assumption provide further detail and evidence to explain and justify our recommendations: • Use of "Under NHSE" as base case value for cost of TAVI valves in cell L5, tab "D3 intervention cost": Supply chain cost / Under NHSE / Supply chain goal / Actual cost of a valve Cost TAVI valve: £20,280.00 / £17,500.00 / £15,000.00 / £17,500 Cost biological valve: £0.00 • Use only reference cost EY21B for average cost of TAVI in both High and Intermediate risk patients (by adjusting equations in Cells E41 and E42 is tab "D3 intervention cost"). • Use of £325 as unit cost of 1 non-ICU day for both TAVI and SAVR rather than assuming these unit costs are different for each procedure • Assume that all 30-day AE costs are included in the reference costs for TAVI and SAVR (i.e. cost of pacemaker implantation, major bleeds and major vascular complications all set to £0 in the model to remove double-counting) • Assume the following length of stay and ICU inputs for TAVI to reflect current clinical practice:	accepted and implemented in the new version of the model: 1. In the base case scenario we are assuming that all the valves are bought at the NHSE price of £17,500 2. We are using now EY21B for cost of TAVI of low-, intermediate- and high-risk people as recommended 3. We decided to use the same non-ICU bed day cost for SAVR and TAVI alike as recommended 4. We are assuming in the base case scenario that all cost of 30 days complications are included in the reference costs, as recommended (though we keep them separated in a sensitivity analysis) 5. ICU and hospital LOS now are informed by the UK TAVI trial, as this better represents the UK practice. ICU and hospital LOS in higher risk groups were calculated using the estimates of hospital resource predictors by Reinhoul

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				○ High Risk: 6 days total LoS with 0.5 days spent in ICU ○ Intermediate Risk: 5 days total LoS with 0.5 days spent in ICU ○ (Keep SAVR LoS data the same given it appears to reflect real-world NHS data for High and Intermediate Risk Patients) • Assume 30-day adverse event rates are taken from forest plots excluding STACCATO and including Evolut Low Risk trials:	(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/) The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. 6. STACCATO was excluded from the trials included and Leon 2021 (PARTNER 3) and Popma 2019 (Evolut) were added instead. In the base case scenario, only trials on 2nd and 3rd generation valve are now used (PARTNER 2, PARTNER 3, Evolut). 7. Ler 2020 was excluded from the evidence and instead the meta-analysis of the trials included in the clinical review was used to inform reintervention treatment effect. A scenario analysis where reintervention treatment effect is close to 1 was tested as well.

SAVR stratification	Look at D4 stratification for the calculation						
Intermediate risk	Probability	r	n	Alpha	Beta	Probabilist	Probabilistic
Stroke	0.054	141	2596	141	2455	0.062	0.057 Beta
Major bleeding	0.281	705	2513	705	1808	0.281	0.286 Beta
Pacemaker implantation	0.063	158	2525	158	2367	0.073	0.068 Beta
Vascular complication	0.030	77	2525	77	2448	0.035	0.039 Beta

Treatment effects (TAVI vs SAVR)							
Treatment effects decisiont tree							
	RR	*LCI (95%)*	*UCI (95%)*	*Log RR*	*Log scale SE*	*Probabilisti*	*Probabilistic*
Stroke	0.91	0.600	1.370	-0.094	0.211	0.680	0.991 Lognorr
Major Bleed	0.51	0.270	0.950	-0.673	0.321	0.547	0.677 Lognorr
Pacemaker Implantation	2.43	1.390	4.250	0.888	0.285	2.048	2.045 Lognorr
Vascular complication	2.82	1.770	4.490	1.037	0.237	2.248	2.476 Lognorr

• Update the reintervention odds ratios for TAVI vs. SAVR to the following to correct the factual inaccuracies in Ler 2020 and include more recent RCT data:

Reintervention	Odds ratio	LCI (95%)	UCI (95%)	*Log mean*	*Log scale SE*	*Probabilisti*	*Probabilistic*
1 year	3.52	1.780	6.960	1.258	0.348	3.874	3.264 Lognormal
2-3 years	3.55	1.860	6.770	1.267	0.330	4.735	3.284 Lognormal
5 years	3.55	1.220	10.380	1.267	0.546	2.984	5.287 Lognormal

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>

Update the moderate/severe PVL rate for TAVI to 3.4%, better reflecting contemporary clinical practice with current TAVI devices.
SCENARIO ANALYSIS FOR 30-DAY and 1-YEAR MORTALITY: Assume the following mortality inputs at 30 days and 1 year:

<table>
<tr><th></th><th>SAVR Baseline mortality at 30 Days</th><th>Odds RatioTAVI vs. SAVR, 30-day mortality</th><th>Odds SAVR,</th></tr>
<tr><td>Current Model High Risk</td><td>0.0537</td><td>0.88</td><td>0.91</td></tr>
<tr><td>Current Model Intermediate Risk</td><td>0.0275</td><td>0.88</td><td>0.91</td></tr>
<tr><td>High Risk-specific</td><td>0.0541</td><td>0.62</td><td>0.86</td></tr>
<tr><td>Intermediate Risk-specific (RCTs only)</td><td>0.0383</td><td>0.96</td><td>0.99</td></tr>
<tr><td>Intermediate Risk-specific (inc. propensity matched studies)</td><td>0.0332</td><td>0.48</td><td>0.71</td></tr>
<tr><td>Low Risk-specific (assumed all other risk-specific inputs are from the IR model)</td><td>0.0220</td><td>0.70</td><td>0.76</td></tr>
</table>
For comparison we also show the scenario where risk-specific baseline SAVR mortality is modelled as in the current model (0.0537 for High Risk and 0.0275 for Intermediate Risk) but the TAVI vs SAVR odds ratios for mortality at 30 days and 1 year are pooled from all published TAVI RCTs
</td><td>
8. PVL after TAVI were informed by a study conducted on 3rd generation Sapien 3 (Herman 2016) reporting lower PVL rates which are in line with the latest BCIS audit on TAVI.

The new results suggest that, at the current price of TAVI, the technology is cost effective in high-risk patients but not in intermediate or low risk patients. The threshold analysis shows that the ICER is very sensitivity to price.

NICE and NHSEI have published a joint implementation strategy alongside the guideline.
</td></tr>
</table>

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>(all risks) excluding STACCATO (Nielson etal., 2012) and including Evolut Low Risk Trial (Popma et al., 2019) (0.79 and 0.90 respectively).

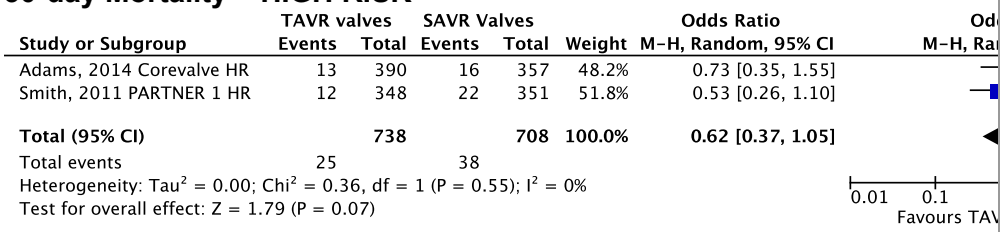
CALCULATED ICERS AFTER CHANGES LISTED ABOVE ARE MADE ALONG WITH IMPLENTATION OF DIFFERENT SCENARIOS FOR MORTALITY AT 30-DAYS AND 1-YEAR (Colour-coding related to NICE-accepted willingness-to-pay threshold of £20,000 – £30,000/QALY):
<table>
<tr><th>Risk Group</th><th>Mortality Scenario</th><th>ICER for 80 Year Olds</th></tr>
<tr><td rowspan="3">HIGH RISK</td><td>CURRENT: High Risk Model provided by NICE for consultation</td><td>£97,023/QALY</td></tr>
<tr><td>REVISED: High Risk-specific baseline SAVR probabilities and TAVI vs SAVR ORs for mortality at 30 days and 1 Year</td><td>£13,226/QALY</td></tr>
<tr><td>FOR COMPARISON: High Risk with pooled TAVI vs SAVR OR for mortality from all published TAVI RCTs excluding STACCATO and including Evolut Low Risk Trial</td><td>£16,667/QALY</td></tr>
<tr><td rowspan="4">INTERMEDIATE RISK</td><td>CURRENT: Intermediate Risk Model provided by NICE for consultation</td><td>£124,565/QALY</td></tr>
<tr><td>REVISED 1: Intermediate Risk-specific baseline SAVR probabilities and TAVI vs SAVR ORs for mortality at 30 days and 1 Year (RCTs only)</td><td>£155,325/QALY</td></tr>
<tr><td>REVISED 2: Intermediate Risk-specific baseline SAVR probabilities and TAVI vs SAVR ORs for mortality at 30 days and 1 Year (inc. RCTS and propensity matched studies using newer valves)</td><td>£18,348/QALY</td></tr>
<tr><td>FOR COMPARISON: Intermediate Risk with pooled TAVI vs SAVR OR for mortality from all published TAVI RCTs excluding STACCATO and including Evolut Low Risk Trial</td><td>£49,487/QALY</td></tr>
<tr><td>LOW RISK</td><td>FOR COMPARISON: Low Risk-specific baseline SAVR probabilities and TAVI vs SAVR ORs for mortality at 30 days and 1-Year (assumed all other risk-specific inputs are from the IR model)</td><td>£22,996/QALY</td></tr>
</table></td><td></td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

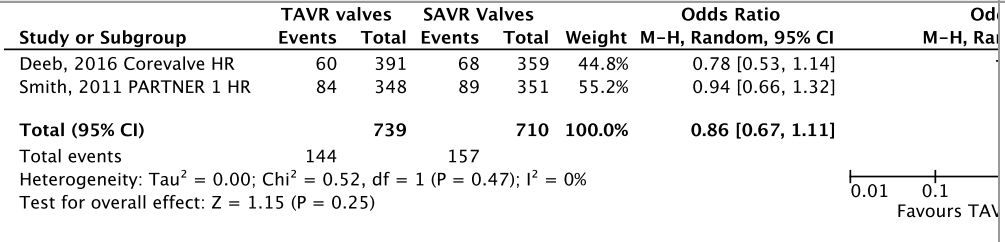
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				SUGGESTED CHANGES <u>NOT IMPLEMENTED</u> IN REVISED BASECASE CALCULATIONS: Please note that there are some changes that we have suggested within our submission however we did not include in the ICER calculations for one of the following reasons: • **Suggestions would be too complex to perform within the consultation period** (e.g. implementation of survival projections & associated calibration to further reflect the overall QALY benefits demonstrated in the RCTs). • **We felt in need of further methodological transparency from NICE to fully understand the assumptions made** (e.g. rehospitalisation). • **We felt our suggested changes could be perceived as "purely for the purpose of using alternative inputs"** rather than factual inaccuracies and so feel it is more appropriate for the committee to perform further literature search, analyses and/or engage with clinical experts before accepting or rejecting our suggestions (currency codes used for SAVR, appropriateness of Martin et al., 2017 to model survival and differentiate survival by age, use of Rodriguez-Gabella et al., 2018 to model baseline SAVR reinterventions, improvements in 30-day Adverse Events since early RCTs, assumption that reintervention rates are equal beyond 5	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				years, appropriateness of QALY assumption for 1 year prior to reintervention) **Acknowledging the range of ICERs derived by the different scenarios, Medtronic strongly recommend that NICE revisit and revise the base case for the high risk patients since these results are particularly contradictive of published data and standard NHS practice. However, in terms of the recommendations (Draft Guideline, page 12, lines 3-7), we would like to reiterate that Medtronic support the largely open definition of suitability for SAVR and TAVI since we do feel this appropriately captures the multifactorial nature of treatment decisions for aortic stenosis patients in the NHS and the need for a multi-disciplinary heart team decision, and we acknowledge that there are still some data gaps for TAVI related to durability. We hope that the range of revised ICERs presented above, along with the considerations outlined but not implemented in the calculations, will give the committee confidence that contemporary TAVI practices are likely cost-effective even in those patients who are, by risk score definition, intermediate and low risk but are deemed unsuitable for SAVR (anatomically, characteristically, circumstantially or preferentially) by a multidisciplinary heart team.**	
Medtronic Limited	Economic Report TAVI	013 & 015		**Odds Ratios for TAVI vs SAVR all-cause mortality at 30 days and 1 year are underestimated, especially for high risk patients.** The economic models for high and intermediate risk assume risk-specific baseline mortality rates for SAVR at 30 days but then the OR applied for TAVI vs SAVR is not risk-specific meaning that the model assumes the	Thank you for your comment. The committee discussed the opportunity of using risk-specific treatment effects but ultimately

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	and Economic Model TAVI And Evidence Review H, Appendix E	421		same difference in mortality between TAVI and SAVR in both high and intermediate risk patients. When we look at the high risk RCTs, we in fact see a greater mortality benefit for TAVI vs SAVR than what is currently being reflected in the economic model. In order to demonstrate this, we have provided the forest plots for high risk RCTs below where it can be observed that the odds ratio is 0.62 at 30 days and 0.86 at 1 year (as compared to the OR = 0.88 at 30 days and OR = 0.91 at 1 year currently used in the economic model): **30-day Mortality – HIGH RISK**  TAVR valves / SAVR Valves / Odds Ratio Study or Subgroup — Events Total Events Total Weight M-H, Random, 95% CI Adams, 2014 Corevalve HR 13 390 16 357 48.2% 0.73 [0.35, 1.55] Smith, 2011 PARTNER 1 HR 12 348 22 351 51.8% 0.53 [0.26, 1.10] **Total (95% CI) 738 708 100.0% 0.62 [0.37, 1.05]** Total events 25 38 Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0% Test for overall effect: Z = 1.79 (P = 0.07) 0.01 0.1 Favours TAV **1-Year Mortality HIGH RISK**	decided against this for 2 main reasons: • The committee agreed that treatment effect is very dependent on TAVI valve generation but less on risk, so they thought it was crucial to capture this first effect • As we are currently using studies on 2nd and 3rd generation valves only to estimate the treatment effects, data from high-risk trials are not used anymore to estimate relative risk (although they are still used for quality of life improvement). Hence, a pragmatic decision was made to stratify the relative treatment effects by valve generation (with 2nd and 3rd valves used in the base case scenario) but not for risk, as stratifying for both was impossible. In the revised version of the model, STACCATO trial was excluded and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 It is also important to note here that the above changes to the odds ratios for high risk mortality are still expected to underestimate the contemporary mortality benefit of TAVI vs SAVR because the high risk trials recruited patients when TAVI was a new and evolving practice, while evidence documents improvements in mortality rates over time (Carrol et al., 2020 and UK TAVI Registry). Among the key reasons for the reduction in overall TAVI mortality is the reduction in transapical vs. transfemoral approach which has shown higher mortality rates (Nielsen 2012, Leon 2016, Gleason 2018) in part enabled by the fact that contemporary TAVI valves and delivery catheters now allow most patients to undergo the safer transfemoral or other approaches. The table below outlines a summary of the access routes used in each RCT thus demonstrating the much higher rates of transfemoral access in contemporary practice.	Evolut included and the in the base case scenarios were only treatment effects estimated from recent trials on 2nd and 3rd generation devices were used. Mortality for all risks at 30 and 1 year in the revised version of the model is fairly aligned with the numbers provided by Medtronic: 30 days: 0.81 1 year: 0.93

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

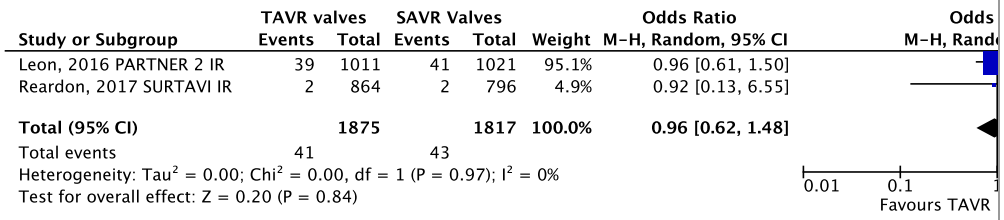
Trial	Risk Group	TAVI Access Route
CoreValve High Risk	High Risk	82.9% Iliofemoral 17.1% Non-iliofemoral
PARTNER 1A	High Risk	70.1% Transfemoral 29.9% Transapical
PARTNER 2A	Intermediate Risk	76.3% Transfemoral 23.7% Transthoracic (174 transapical/62 transthoracic)
SURTAVI	Intermediate Risk	93.6% Transfemoral 4.1% Direct Aortic 2.3% Subclavian
NOTION	Low Risk	96.5% Transfemoral 3.5% subclavian
PARTNER 3	Low Risk	100% Transfemoral
Evolut Low Risk	Low Risk	99% transfemoral 0.6% subclavian 0.4% direct aortic

The intermediate risk trials are also now outdated. PARTNER 2A in particular included a high proportion of transapical TAVI procedures, and both trials used predominantly 1st generation TAVI valves (Leon 2016 and Reardon 2017). Whilst the trials did demonstrate non-inferiority, the risk-specific forest plots for this group show odds ratios of 0.96 at 30-days and of 0.99 at 1 year:

30-day Mortality – INTERMEDIATE RISK

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

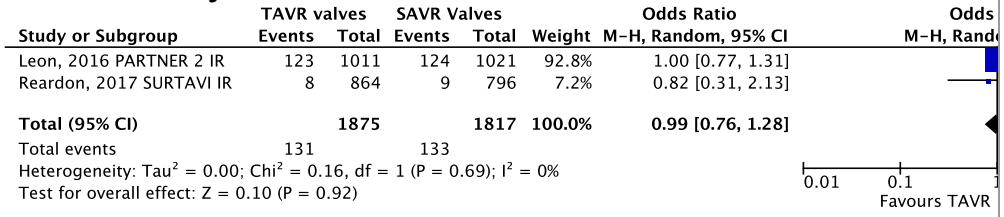
Stakeholder	Document	Page No	Line No	Comments	Developer's response



Study or Subgroup	TAVR valves Events	Total	SAVR Valves Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds M-H, Rand
Leon, 2016 PARTNER 2 IR	39	1011	41	1021	95.1%	0.96 [0.61, 1.50]	
Reardon, 2017 SURTAVI IR	2	864	2	796	4.9%	0.92 [0.13, 6.55]	
Total (95% CI)		**1875**		**1817**	**100.0%**	**0.96 [0.62, 1.48]**	
Total events	41		43				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 0.20 (P = 0.84)

1-Year Mortality - INTERMEDIATE RISK

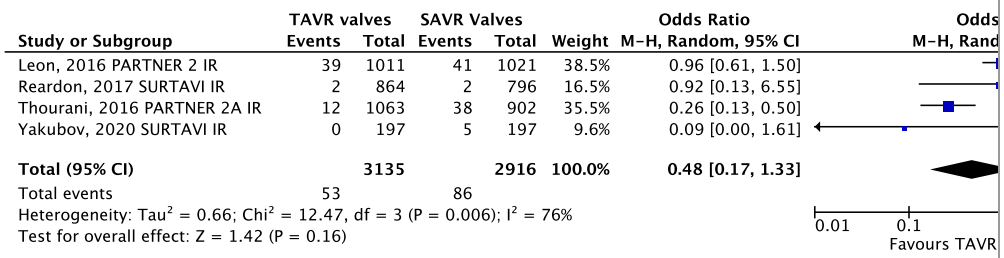


Study or Subgroup	TAVR valves Events	Total	SAVR Valves Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds M-H, Rand
Leon, 2016 PARTNER 2 IR	123	1011	124	1021	92.8%	1.00 [0.77, 1.31]	
Reardon, 2017 SURTAVI IR	8	864	9	796	7.2%	0.82 [0.31, 2.13]	
Total (95% CI)		**1875**		**1817**	**100.0%**	**0.99 [0.76, 1.28]**	
Total events	131		133				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 0.10 (P = 0.92)

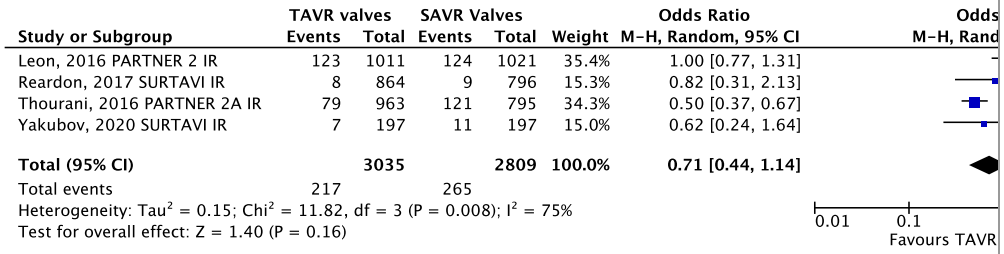
There are some propensity score matched data that indicates improvements in mortality outcomes with new valve iterations in intermediate risk patients. The SURTAVI Continued Access Study (CAS) was a single-arm study following the SURTAVI RCT and enrolled 290 patients; 252 of which were implanted with the second generation Evolut R TAVI valve (compared to the SURTAVI RCT where 84% of patients had the 1st generation CoreValve implanted). Yakubov et al. 2020 used the SURTAVI CAS data to perform a propensity-matched comparison of Evolut-R with SAVR patients from the SURTAVI RCT and demonstrated a higher mortality benefit of TAVI in intermediate risk patients at 30 days and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1 year. Thourani et al., 2016 also published a propensity matched comparison of TAVI vs SAVR in intermediate-risk patients using the newer-generation SAPIEN 3 TAVI valve. Whilst we understand that NICE are likely to favour RCT data over propensity matched studies, we believe the below forest plots help to demonstrate that newer TAVI valve iterations have shown improved patient mortality outcomes that could be considered in the economic model: **30-day Mortality – INTERMEDIATE RISK** (including Yakubov, 2020 and Thourani 2016)  **1-Year Mortality INTERMEDIATE RISK** (including Yakubov, 2020 and Thourani 2016)	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

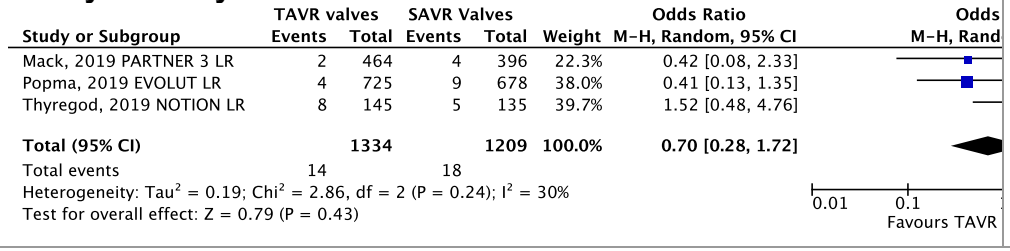


Study or Subgroup	TAVR valves Events	Total	SAVR Valves Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds M-H, Rand
Leon, 2016 PARTNER 2 IR	123	1011	124	1021	35.4%	1.00 [0.77, 1.31]	
Reardon, 2017 SURTAVI IR	8	864	9	796	15.3%	0.82 [0.31, 2.13]	
Thourani, 2016 PARTNER 2A IR	79	963	121	795	34.3%	0.50 [0.37, 0.67]	
Yakubov, 2020 SURTAVI IR	7	197	11	197	15.0%	0.62 [0.24, 1.64]	
Total (95% CI)		**3035**		**2809**	**100.0%**	**0.71 [0.44, 1.14]**	
Total events	217		265				

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 11.82$, df = 3 (P = 0.008); $I^2 = 75\%$
Test for overall effect: Z = 1.40 (P = 0.16)

Page 47, lines 10 & 11 of the Economic Report states that: "Although people at low risk were not studied in this analysis, we expect TAVI to be even less cost effective in this category of patients." However, Medtronic would strongly urge NICE to explore the mortality reported in the low risk RCTs because Popma et al., 2019 and Mack et al., 2019/Leon et al., 2021 closely represent contemporary clinical practice and, in fact found mortality benefits of TAVI similar to, and potentially even greater than, those seen in the early high risk RCTs:

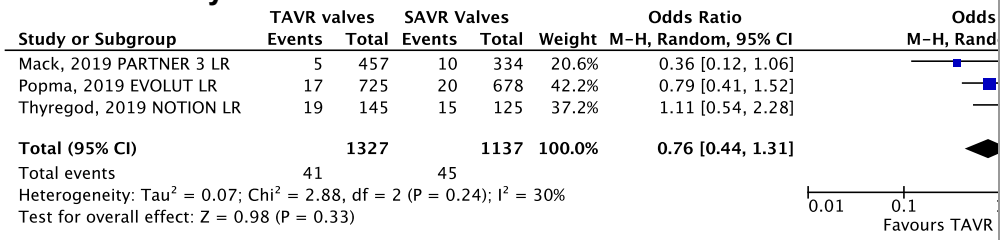
30-day Mortality – LOW RISK



Study or Subgroup	TAVR valves Events	Total	SAVR Valves Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds M-H, Rand
Mack, 2019 PARTNER 3 LR	2	464	4	396	22.3%	0.42 [0.08, 2.33]	
Popma, 2019 EVOLUT LR	4	725	9	678	38.0%	0.41 [0.13, 1.35]	
Thyregod, 2019 NOTION LR	8	145	5	135	39.7%	1.52 [0.48, 4.76]	
Total (95% CI)		**1334**		**1209**	**100.0%**	**0.70 [0.28, 1.72]**	
Total events	14		18				

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.86$, df = 2 (P = 0.24); $I^2 = 30\%$
Test for overall effect: Z = 0.79 (P = 0.43)

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1-Year Mortality LOW RISK  The current methodology used by NICE to define the baseline SAVR mortality at 30 days is somewhat unclear and appear to be underestimated for both risk groups. Of course, if the ORs are changed to be risk-specific within the model, the baseline SAVR mortalities at 30 days will also need adjusting. Using the forest plots outlined above, we have re-calculated the following baseline SAVR mortalities at 30 days:	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

	TAVI Events	Total TAVI	SAVR Events	Total SAVR	Weight	Weighted Average SAVR Mortality 30 days
LOW RISK						
Mack 2019	2	464	4	396	22.30%	0.0023
Popma 2019	4	725	9	678	38.00%	0.0050
Thyregod 2015	8	145	5	135	39.70%	0.0147
					Baseline SAVR:	**0.0220**
INTERMEDIATE RISK (RCT ONLY)						
Leon 2016	39	1011	41	1021	95.10%	0.0382
Reardon 2017	2	864	2	796	4.90%	0.0001
					Baseline SAVR:	**0.0383**
INTERMEDIATE RISK (RCT + PROPENSITY MATCHED)						
Leon 2016	39	1011	41	1021	38.5%	0.0155
Reardon 2017	2	864	2	796	16.5%	0.0004
Thourani 2016	12	1063	38	902	35.3%	0.0149
Yakubov 2020	0	197	5	197	9.6%	0.0024
						0.0332
HIGH RISK						
Adams 2014	13	390	16	357	48.20%	0.0216
Smith 2011	12	348	22	351	51.80%	0.0325
					Baseline SAVR:	**0.0541**

In summary, the table below outlines the current and suggested assumptions related to mortality at 30 days and 1 year:

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

	SAVR Baseline mortality at 30 Days	Odds RatioTAVI vs. SAVR, 30-day mortality	Odds RatioTAVI vs. SAVR, 1-year mortality
Current Model High Risk	0.0537	0.88	0.91
Current Model Intermediate Risk	0.0275	0.88	0.91
High Risk-specific	0.0541	0.62	0.86
Intermediate Risk-specific (RCTs only)	0.0383	0.96	0.99
Intermediate Risk-specific (inc. propensity matched studies)	0.0332	0.48	0.71
Low Risk-specific (assumed all other risk-specific inputs are from the IR model)	0.0220	0.70	0.76

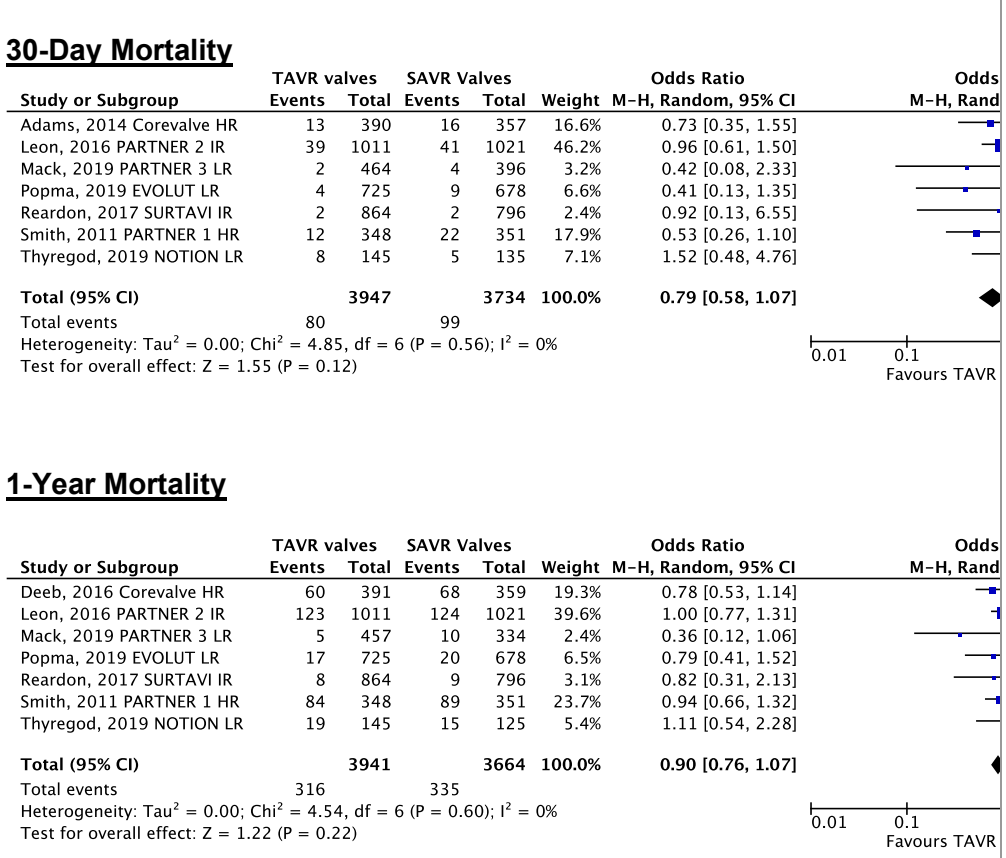
By replacing the existing odds ratios with the risk-specific ones outlined above for high, intermediate, and low risk, this would have significant impact on the ICERs, including a decrease in the ICER by close to 50% in high risk patients, yielding a much different cost-effectiveness finding.

Whilst Medtronic strongly feel the most appropriate approach is to model mortality for each risk group separately as outlined in detail above, should NICE decide to continue with their original approach of pooling RCTs at all risk groups for mortality, Medtronic feel very strongly that the STACCATO trial should be excluded from any data-pooling and the Evolut Low Risk trial should be included.

The STACCATO trial (Nielson et al., 2012) was a randomised trial of transapical TAVI versus SAVR. The transapical approach is now only rarely used in the NHS and therefore the inclusion of the STACCATO Trial

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				is not reflective of current clinical practice. The other RCTs (except PARTNER 3) did not exclude the transapical approach but were predominantly transfemoral and therefore are more likely to better reflect true practice in terms of the mix of access approaches used for TAVI. In addition, we notice that the Evolut Low Risk trial (Popma et al., 2019) has not been included in any of the forest plots. We believe this is because NICE considered surgical approach for SAVR to be unclear/mixed invasiveness and therefore analysed this trial in separate forest plots under Appendix E, E1.4 Transcatheter replacement vs. surgery replacement (unclear/mixed invasiveness) (page 428, Evidence Review H/8). Medtronic would like to inform NICE that in the SAVR arm of the Evolut Low Risk trial (Popma et al., 2019), 33.9% of the patients had a minimally invasive procedure (hemi-sternotomy, mini-sternotomy or right anterior sternotomy). Therefore, in the same way as the Partner 3 trial (Mack et al, 2019), in which 24.3% of SAVR patients also had a minimally invasive procedure, it would be legitimate that the Evolut Low Risk trial (Popma et al., 2019) be included in the stratum "transcatheter replacement vs. standard surgery replacement" with forest plots being updated accordingly. Moreover, this would be more appropriate for the purpose of economic modelling because this study design in fact means that the trial is reflective of current clinical practice since cardiac surgeons were allowed to choose the preferred SAVR approach as they can in real-world practice. For completion, we would therefore like to provide updated forest plots for mortality at 30 days and 1 year, including all relevant RCTs as outlined above:	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

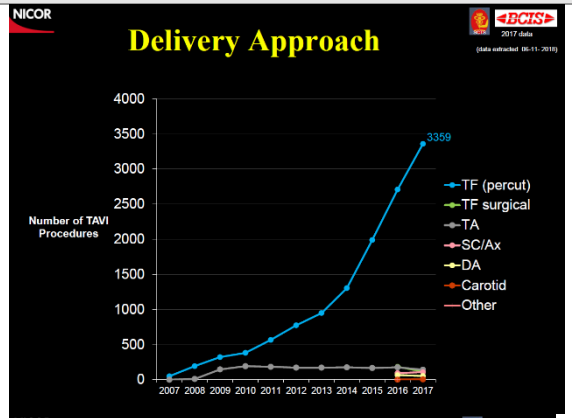
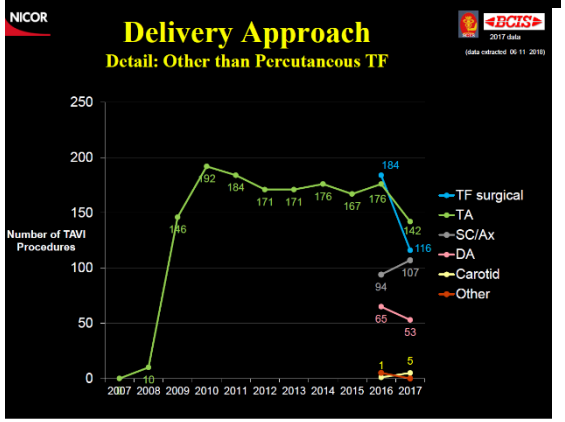
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				These lower ORs, if used, would impact the resultant ICERs in both the High Risk and Intermediate Risk models and we strongly recommend that NICE explore this in cost-effectiveness analysis. **REFERENCES:** • Carroll et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement, J Am Coll Cardiol 2020; 21: 2492 – 516 • Yakubov SJ, Van Mieghem NM, Reardon MJ, Serruys PW, Gada H, Mumtaz M, et al. Propensity-Matched Comparison of Evolut-R Transcatheter Aortic Valve Implantation With Surgery in Intermediate-Risk Patients (from the SURTAVI Trial). The American journal of cardiology. 2020;131:82-90. • Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. The Lancet. 2016;387(10034):2218-25. • Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. New England Journal of Medicine. 2019;380(18):1706-15. • Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine. 2016;374(17):1609-20 • Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. Journal of	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the American College of Cardiology. 2018;72(22):2687-96.Mack 2019 • Thyregod H, Ihlemann N, Jørgensen T, Nissen H, Kjeldsen B, Petursson P, et al. Five-Year Clinical and Echocardiographic Outcomes From the NOTION Randomized Clinical Trial in Patients at Lower Surgical Risk. Circulation. 2019;139(24):2714-23. • Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis. New England Journal of Medicine. 2014;370(19):1790-8. • Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. EuroIntervention. 2012; 8(3):383-389 • Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine. 2017;376(14):1321-31. • Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. New England Journal of Medicine. 2011;364(23):2187-98.	
Medtronic Limited	Economic Report	013 & 015		**Forest plots for 30-day stroke, pacemaker, vascular complications and major bleeding should, at a minimum, exclude the STACCATO trial (Nielson et al., 2012) and include the Evolut Low Risk Trial (Popma et al., 2019). Ideally consideration should be taken for**	Thank you for your comment. The committee acknowledge that technological improvement was not

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	TAVI Economic Model TAVI and Evidence Review H, Appendix E	419		**improvements in adverse event rates for TAVI since the early RCTs along with the dependence/independence of these outcomes relating to risk group.** The baseline SAVR probabilities and applied odds ratios for TAVI vs. SAVR for adverse events at 30 days are derived from the forest plots available in Evidence Review H/8. These forest plots include the STACCATO trial (Nielson et al., 2012) which should be excluded because it was a randomised trial of transapical TAVI versus SAVR. The transapical approach is not a common approach, as shown below in the UK TAVI registry and therefore the inclusion of the STACCATO Trial is not reflective of current clinical practice. The other RCTs (except PARTNER 3) did not exclude the transapical approach but were predominantly transfemoral and therefore are more likely to reflect true practice in terms of the mix of access approaches used for TAVI. The below data from the UK TAVI Registry confirms the very infrequent use of the transapical approach in contemporary TAVI practice in the UK:	fully captured in the model and decided to now include only trials of 2nd and 3rd generations: PARTNER 2, PARTNER 3 and Evolut. Trials focusing on old valves e.g., Partner 1A and CoreValve High Risk were excluded from the base case but still used in the scenario analysis. The STACCATO trial was excluded from all the scenarios as the transapical approach is not relevant for this analysis. Baseline risks after TAVI are not calculated anymore using a weighted average of all the events occurring across the trials but based on the latest NICOR TAVI audit. This ensures that the TAVI adverse event probabilities reflect current practice in the UK. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				  In addition, we notice that the Evolut Low Risk (LR) trial (Popma et al., 2019) has not been included in the forest plots. We believe this is because	at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				NICE considered surgical approach for SAVR to be unclear/mixed invasiveness and therefore analysed this trial in separate forest plots under Appendix E, E1.4 Transcatheter replacement vs. surgery replacement (unclear/mixed invasiveness) (page 428, Evidence Review 8). Medtronic would like to inform NICE that in the SAVR arm of the Evolut Low Risk trial (Popma et al., 2019), 33.9% of the patients had a minimally invasive procedure (hemi-sternotomy, mini-sternotomy or right anterior sternotomy). Therefore, in the same way as the Partner 3 trial (Mack et al, 2019), in which 24.3% of SAVR patients also had a minimally invasive procedure, it would be legitimate that the Evolut Low Risk trial (Popma et al., 2019) be included in the stratum "transcatheter replacement vs. standard surgery replacement" with forest plots being updated accordingly. Moreover, this would be more appropriate for the purpose of economic modelling because this study design in fact means that the trial is reflective of current clinical practice since cardiac surgeons were allowed to choose the preferred SAVR approach as they can in real-world practice. Below we have repeated the forest plots to exclude STACCATO and include Evolut Low Risk: **Updated Intervention-related stroke or TIA (with STACCATO excluded and Evolut LR Included):**	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

Study or Subgroup	Transcatheter replacement Events	Total	Stan. surgery replacement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adams 2014 (CoreValve: high risk)	19	390	22	357	15.7%	0.79 [0.44, 1.44]
EVOLUT LR	29	730	30	684	18.5%	0.91 [0.55, 1.49]
Leon 2016 (PARTNER 2: intermediate risk)	64	1011	65	1021	24.1%	0.99 [0.71, 1.39]
Mack 2019 (PARTNER 3: low risk)	3	496	11	454	5.6%	0.25 [0.07, 0.89]
Reardon 2017 (SURTAVI: intermediate risk)	30	879	46	867	20.1%	0.64 [0.41, 1.01]
Smith 2011 (PARTNER 1A: high risk)	19	348	8	351	11.0%	2.40 [1.06, 5.40]
Thyregod 2015 (NOTION: low risk)	4	139	4	135	5.0%	0.97 [0.25, 3.81]
Total (95% CI)		**3993**		**3869**	**100.0%**	**0.88 [0.63, 1.23]**
Total events	168		186			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 12.14$, df = 6 (P = 0.06); $I^2 = 51\%$
Test for overall effect: Z = 0.76 (P = 0.45)

0.01
Favour

Updated Intervention-related Pacemaker implantation (with STACCATO excluded and Evolut LR included):

Study or Subgroup	Transcatheter replacement Events	Total	Stan. surgery replacement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adams 2014 (CoreValve: high risk)	76	390	25	357	15.8%	2.78 [1.81, 4.27]
EVOLUT LR	125	730	41	684	16.7%	2.86 [2.04, 4.00]
Leon 2016 (PARTNER 2: intermediate risk)	85	1011	68	1021	16.9%	1.26 [0.93, 1.72]
Mack 2019 (PARTNER 3: low risk)	32	496	18	454	14.4%	1.63 [0.93, 2.86]
Reardon 2017 (SURTAVI: intermediate risk)	224	864	53	796	17.1%	3.89 [2.93, 5.17]
Smith 2011 (PARTNER 1A: high risk)	13	348	12	351	12.2%	1.09 [0.51, 2.36]
Thyregod 2015 (NOTION: low risk)	46	139	2	135	6.9%	22.34 [5.53, 90.20]
Total (95% CI)		**3978**		**3798**	**100.0%**	**2.47 [1.55, 3.94]**
Total events	601		219			

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 46.15$, df = 6 (P < 0.00001); $I^2 = 87\%$
Test for overall effect: Z = 3.80 (P = 0.0001)

0.01
Favour

Updated Intervention-related Major bleeding (with STACCATO excluded and Evolut LR included):

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

Study or Subgroup	Transcatheter replacement Events	Total	Stan. surgery replacement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adams 2014 (CoreValve: high risk)	109	390	123	357	15.1%	0.81 [0.65, 1.00]
EVOLUT LR	18	730	51	684	13.7%	0.33 [0.20, 0.56]
Leon 2016 (PARTNER 2: intermediate risk)	105	1011	442	1021	15.2%	0.24 [0.20, 0.29]
Mack 2019 (PARTNER 3: low risk)	13	496	61	454	13.3%	0.20 [0.11, 0.35]
Reardon 2017 (SURTAVI: intermediate risk)	104	858	73	784	14.9%	1.30 [0.98, 1.73]
Smith 2011 (PARTNER 1A: high risk)	32	348	67	351	14.4%	0.48 [0.32, 0.71]
Thyregod 2015 (NOTION: low risk)	16	139	28	135	13.4%	0.55 [0.31, 0.98]
Total (95% CI)		**3972**		**3786**	**100.0%**	**0.47 [0.26, 0.83]**
Total events	397		845			

Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 133.03$, df = 6 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: Z = 2.58 (P = 0.010)

0.01
Favours

Updated Intervention-related Major Vascular Complication (with STACCATO excluded and Evolut LR included):

Study or Subgroup	Transcatheter replacement Events	Total	Stan. surgery replacement Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Adams 2014 (CoreValve: high risk)	23	390	6	357	12.5%	3.51 [1.45, 8.52]
EVOLUT LR	27	730	21	684	17.6%	1.20 [0.69, 2.11]
Leon 2016 (PARTNER 2: intermediate risk)	80	1011	51	1021	21.1%	1.58 [1.13, 2.23]
Mack 2019 (PARTNER 3: low risk)	10	496	6	454	11.1%	1.53 [0.56, 4.16]
Reardon 2017 (SURTAVI: intermediate risk)	52	864	9	796	15.3%	5.32 [2.64, 10.73]
Smith 2011 (PARTNER 1A: high risk)	38	348	11	351	16.0%	3.48 [1.81, 6.70]
Thyregod 2015 (NOTION: low risk)	8	145	2	135	6.5%	3.72 [0.81, 17.23]
Total (95% CI)		**3984**		**3798**	**100.0%**	**2.40 [1.52, 3.78]**
Total events	238		106			

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 17.94$, df = 6 ($P = 0.006$); $I^2 = 67\%$
Test for overall effect: Z = 3.76 (P = 0.0002)

0.01
Favou

For completion, if the ORs are adjusted to exclude STACCATO and include Evolut Low Risk, the baseline SAVR rate will also need adjusting accordingly. Below we have used the weighting from the forest plots to calculate these:

	TAVI Events	Total TAVI	SAVR Events	Total SAVR	Weight	Weighted Average Baseline SAVR 30 days
STROKE OR TIA						
Adams 2014	19	390	22	357	15.70%	0.0097
Popma 2019	29	730	30	684	18.50%	0.0081
Leon 2016	64	1011	65	1021	24.10%	0.0153
Mack 2019	3	496	11	454	5.60%	0.0014
Reardon 2017	30	879	46	867	20.10%	0.0107
Smith 2011	19	348	8	351	11.00%	0.0025
Thyregod 2015	4	139	4	135	5.00%	0.0015
				Baseline SAVR:		**0.0491**
PACEMAKER						
Adams 2014	76	390	25	357	15.80%	0.0111
Popma 2019	125	730	41	684	16.70%	0.0100
Leon 2016	85	1011	68	1021	16.90%	0.0113
Mack 2019	32	496	18	454	14.40%	0.0057
Reardon 2017	224	864	53	796	17.10%	0.0114
Smith 2011	13	348	12	351	12.20%	0.0042
Thyregod 2015	46	139	2	135	6.90%	0.0010
				Baseline SAVR:		**0.0546**
MAJOR BLEEDING						
Adams 2014	109	390	123	357	15.10%	0.0520
Popma 2019	18	730	51	684	13.70%	0.0102
Leon 2016	105	1011	442	1021	15.20%	0.0658
Mack 2019	13	496	61	454	13.30%	0.0179
Reardon 2017	104	858	73	784	14.90%	0.0139
Smith 2011	32	348	67	351	14.40%	0.0275
Thyregod 2015	16	139	28	135	13.40%	0.0278
				Baseline SAVR:		**0.2151**
MAJOR VASCULAR COMPLICATION						
Adams 2014	23	390	6	357	12.50%	0.0021
Popma 2019	27	730	21	684	17.60%	0.0054
Leon 2016	80	1011	51	1021	21.10%	0.0105
Mack 2019	10	496	6	454	11.10%	0.0015
Reardon 2017	52	864	9	796	15.30%	0.0017
Smith 2011	38	348	11	351	16.00%	0.0050
Thyregod 2015	8	145	2	135	6.50%	0.0010
				Baseline SAVR:		**0.0272**

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				By replacing the existing risk ratios with the updated ones as highlighted in green below, there is a modest impact on the ICER however we feel strongly that this is an important adjustment that needs to be made:	

SAVR stratification	Look at D4 stratification for the calculation							
Intermediate risk	Probability	r	n	Alpha	Beta	Probabilist	Probabilistic	
Stroke	0.054	141	2596	141	2455	0.062	0.057 Beta	0.04
Major bleeding	0.281	705	2513	705	1808	0.281	0.286 Beta	0.21
Pacemaker implantation	0.063	158	2525	158	2367	0.073	0.068 Beta	0.05
Vascular complication	0.030	77	2525	77	2448	0.035	0.039 Beta	0.02

Treatment effects (TAVI vs SAVR)							
Treatment effects decisiont tree							
	RR	*LCI (95%)*	*UCI (95%)*	*Log RR*	*Log scale SE*	Probabilisti	Probabilistic
Stroke	0.91	0.600	1.370	-0.094	0.211	0.680	0.991 Lognormal
Major Bleed	0.51	0.270	0.950	-0.673	0.321	0.547	0.677 Lognormal
Pacemaker Implantation	2.43	1.390	4.250	0.888	0.285	2.048	2.045 Lognormal
Vascular complication	2.82	1.770	4.490	1.037	0.237	2.248	2.476 Lognormal

It is also important to note that the use of all published RCTs to model these adverse events is unlikely to be reflective of contemporary clinical practice due to significant improvements in TAVI procedure and outcomes over time. The High Risk TAVI versus SAVR RCTs, Partner 1A and CoreValve High Risk, began recruitment of patients in 2007 and 2010, respectively, and both used 1st generation TAVI valves. In contrast the two low risk trials, Partner 3 and Evolut Low Risk, both began patient recruitment in 2016 and predominantly –although not exclusively—used 3rd generation TAVI valves. The UK TAVI registry has documented changes in outcomes and NHS clinical practice over this time period; however, it has

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				not reported outcomes by risk group. Conversely, the STS-ACC TVT Registry has reported data on 276,316 patients undergoing TAVI from 2011 to 2019 and therefore provides robust evidence to demonstrate improvements in real-world TAVI outcomes over time. The registry also reports these outcomes by risk which facilitates an assessment of which outcomes are/ are not affected by risk group. **PERMANENT PACEMAKER** Carroll et al., 2020 shows that in 2019, the 30-day pacemaker rate was 11.8% in the high/ extreme-risk cohort, 10.3% in the intermediate-risk cohort, and 8.2% in the low-risk cohort. This indicates that high risk patients appear to be at a higher risk of permanent pacemaker implantation. At the same time a temporal decline in pacemaker rates from a peak of 15.1% in 2015 down to the 2019 rate of 10.8% was also demonstrated. The economic model uses ORs to derive a pacemaker rate of 15.3% for TAVI which may be over-estimated compared to current clinical practice in high and intermediate risk patients. We would recommend using the most recent UK TAVI Registry data to understand if the pacemaker rate is representative of current NHS practice, leading to potential overestimation of cost in the TAVI strategy. **STROKE** Data from Carroll et al. 2020 demonstrate that 30-day stroke rates have decreased nominally from 2011-2013 (2.75%) to more recent experience in 2019 (2.3%). 30-day stroke rates in 2019 for the high/extreme-risk cohort	

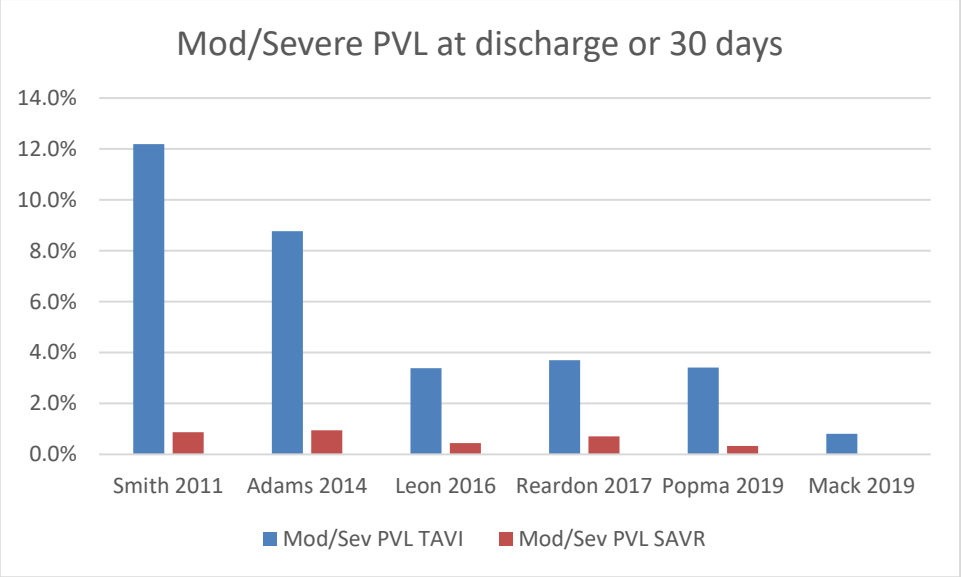
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				were 2.7%, and 1.9% for both the intermediate and low risk cohort. This indicates that the stroke risk in high risk patients is elevated compared to the risk in intermediate and low risk patients. The economic model uses ORs to derive a stroke rate of 4.8% for TAVI which – in light of these data – may be over-estimating event rates compared to current clinical outcomes in high and intermediate risk patients. **VASCULAR COMPLICATIONS** Data from Carroll et al. 2020 demonstrate that thirty-day major vascular access site complications have declined to 1.3%. The 2019 rate was highest in the high/extreme-risk cohort at 1.5%, as compared to 1.1% in the intermediate risk cohort and 0.7% in the low-risk cohort. Vascular complication rates need to be interpreted in the context of the major shift to predominantly femoral access over the years. The economic model uses ORs to derive a vascular complication rate of 7.35% for TAVI which seems to over-estimate the complication rate considering evidence from current clinical practice in high and intermediate risk patients. Further, it is evident from the ORs for the individual RCTs that the difference in the rate of vascular complications between TAVI and SAVR is much lower in those trials that predominantly used 2nd and 3rd generation devices (Popma 2019: OR = 1.20, Mack 2019: OR = 1.53, Leon 2016: OR = 1.58) compared to the trials where the TAVI devices were predominantly 1st generation with larger delivery catheters often needing larger fixed	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				sheaths (Adams 2014: OR = 3.51, Reardon 2017: OR = 5.32, Smith 2011: OR = 3.48, Thyregod 2015: OR: 3.72). **MAJOR BLEEDING** Data from Carroll et al., 2020 demonstrates that use of blood transfusion has declined from 18.2% during the earlier TAVI experience (2011-2013) to 5.8% in 2019. Rates of life-threatening/disabling bleeding during index hospitalization declined from 6.3% in the earlier TAVI experience to 1.8% in 2019. In 2019, the high/extreme-risk cohort had an in-hospital life-threatening/disabling bleeding rate of 2.3%, whereas the intermediate-risk cohort rate was 1.45%, and the low-risk cohort rate was 1.2%. The in-hospital life-threatening/ disabling bleeding rate for those at high/ extreme risk has declined from 6.3% during the early TAVI experience to 2.3% for 2019. **REFERENCES:** • Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. New England Journal of Medicine. 2019;380(18):1706-15. • Carroll et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement, J Am Coll Cardiol 2020; 21: 2492 – 516 • Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve	

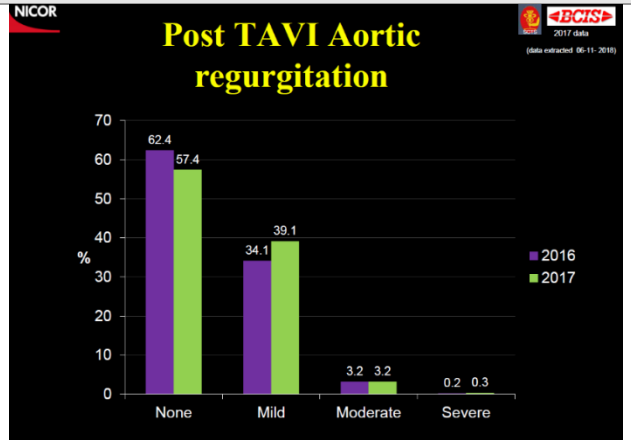
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				replacement in operable elderly patients with aortic stenosis: the STACCATO trial. EuroIntervention. 2012; 8(3):383-389	
Medtronic Limited	Economic Report TAVI And Economic Model TAVI	014		**The economic model assumes a 30-day moderate/severe PVL rate of 4.63% which we believe is overestimated and irreflective of contemporary practice.** It is well documented that the rates of moderate/severe paravalvular leaks have significantly improved with the evolution of TAVI devices and changes in clinical practice. The STS-ACC TVT Registry from 2011 to 2019 has reported data on 276,316 patients undergoing TAVI and therefore provides robust evidence to demonstrate improvements in real-world TAVI outcomes over time. Carroll et. al 2020 demonstrate that moderate/severe Aortic Regurgitation (includes PVL) 30-days post-TAVI was present in 8.0% of patients in the early TAVI experience and has fallen to 1.6% in 2019. In 2019, the rate in the high/extreme-risk cohort was 1.7%, in the intermediate-risk cohort 1.4%, and in the low-risk cohort 1.4%. The 30-day rate of moderate/severe AR for those classified as high-extreme risk has decreased from the early TAVI experience (8.1%) to 2019 (1.75%). When looking at the published RCT data in order of publication date, an improvement in mod/sev PVL rates is clearly achieved over time.	Thank you for your comment. We revised the model to account for TAVI technological improvement. Baseline PVL rates now come from two studies on 3rd generation Sapien 3 valve conducted on high- (Herman 2016) and intermediate/low-risk population (Wendler 2017). These studies report a considerably lower PVL rate (2.7% moderate or severe) which is in line with the rate reported in the TAVI registry. The model is not assuming that all reinterventions are due to SVD. The baseline risks for reintervention after surgery are based on the paper of Rodriguez-Gabella 2018 which reported observed reinterventions occurring during a time period of 12 years, regardless of their causes. Hence, the model is including

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 The moderate/severe PVL rates reported in the UK TAVI Registry are aligned with the more recent RCT data:	reintervention occurring for reasons other than SVD. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 To provide a practical explanation of why we see reduced PVL rates, we wish to explain the evolution of TAVI devices and temporal changes in TAVI implantation/sizing technique, for example aortic annulus sizing was previously performed by echocardiography and not computed tomography. The 1st Generation CoreValve was not recapturable meaning that the valve could not be repositioned once deployed and therefore if the valve was deployed in a position that was causing PVL, it could not be repositioned. The 3rd Generation Evolut PRO valve has a porcine pericardial tissue outer skirt (wrap) around the outer sealing zone of the Nitinol frame, designed to provide advanced sealing by increasing surface contact with native anatomy to reduce the incidence of paravalvular leak (PVL). The table below describes the features of the different generations of Medtronic TAVI valve which were designed specifically or in-part to reduce PVL:	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

	CoreValve™	Evolut™ R	E
Generation	1st	2nd	
CE Mark received	2007	2014 (2016, 2017)	
External pericardial wrap	No	No	
Can be completely recaptured for repositioning	No	Yes	
RCTs using each valve	• 100% of TAVI valves used in CoreValve High Risk trial • 100% of TAVI valves used in NOTION • 84% of TAVI valves used in SURTAVI	• 16% of TAVI valves used in SURTAVI Trial • 22% of TAVI valves used in Evolut Low Risk Trial	•

It should also be considered that patients at highest risk of moderate/severe PVL are those with heavily calcified native valves and/or aortic roots (Martino et al., 2017) and so it is possible to use the pre-operative CT scans to predict which patients are likely to result in mod/sev PVL and therefore in real-world practice, and because the impact of mod/sever PVL is understood, TAVI would only be considered in patients who are not suitable for SAVR as determined by multidisciplinary heart team.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We know from the randomised clinical trials that patients often have their PVL fixed via reintervention (Makkar 2020, Pibarot 2020, Holy 2018). The costs of these have already been modelled by NICE within the reintervention section of the model, albeit under the inaccurate assumption that all reinterventions reported in RCTs were for SVD. All matters considered, Medtronic recommend that NICE use the UK TAVI registry to model the 30-day incidence of mod/severe PVL of 3.5% in TAVI patients *or* use only the more recent RCT data as per the forest plot below which calculates a very similar TAVI mod/sev PVL rate of 3.4% alongside a SAVR rate of 0.51%. **Revised forest plot for Moderate/Severe PVL at discharge or 30-days:** TAVR valves / SAVR valves / Odds Ratio Study or Subgroup — Events — Total — Events — Total — Weight — M-H, Random, 95% CI Mack, 2019 PARTNER 3 LR — 4 — 496 — 0 — 454 — 4.5% — 8.31 [0.45, 154.69] Makkar, 2020 PARTNER 2 IR — 32 — 945 — 4 — 896 — 35.2% — 7.82 [2.75, 22.19] Popma, 2019 EVOLUT LR — 24 — 703 — 2 — 608 — 18.3% — 10.71 [2.52, 45.50] Reardon, 2017 SURTAVI IR — 29 — 784 — 5 — 707 — 42.0% — 5.39 [2.08, 14.01] **Total (95% CI)** — **2928** — **2665** — **100.0%** — **7.10 [3.83, 13.19]** Total events — 89 — 11 Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.68$, df = 3 (P = 0.88); $I^2 = 0\%$ Test for overall effect: Z = 6.21 (P < 0.00001) 0.01 — 0.1 Favo Revised baseline probabilities calculated from the forest plot above:	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

Study	Reference	Weight	TAVI Events	Total TAVI	Mod/Sev PVL TAVI	Weighted Average TAVI Probability	SAVR Events
Mod/Sev PVL at Discharge or 30 Days							
PARTNER 2	Makkar 2020	35.2%	32	945	3.4%	1.2%	4
SURTAVI	Reardon 2017	42.0%	29	784	3.7%	1.6%	5
Evolut LR	Popma 2019	18.3%	24	703	3.4%	0.6%	2
PARTNER 3	Mack 2019	4.5%	4	496	0.8%	0.0%	0
						3.4%	

By adjusting this mod/severe PVL parameter only in the High Risk, 80 years old model for example, this would have very little impact on incremental costs however the incremental QALYs would increase, thus impacting the resultant ICER.

REFERENCES:

- Carroll et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement, J Am Coll Cardiol 2020; 21: 2492 – 516
- Pibarot P, Ternacle J, Jaber WA, Salaun E, Dahou A, Asch FM, et al. Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. Journal of the American College of Cardiology. 2020;76(16):1830-43
- Holy EW, Kebernik J, Abdelghani M, et al. Long-term durability and hemodynamic performance of a self-expanding transcatheter heart valve beyond 5 years after implantation: A prospective observational study applying the standardized definitions of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				structural deterioration and valve failure. EuroIntervention 2018; doi:10.4244/EIJ-D-18-00041. • Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. New England Journal of Medicine. 2020;382(9):799-809. • Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. New England Journal of Medicine. 2019;380(18):1706-15. • Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine. 2017;376(14):1321-31. • Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. New England Journal of Medicine. 2019;380(18):1695-705. • Martino et al., Relation between calcium burden, echocardiographic stent frame eccentricity and paravalvular leakage after corevalve transcatheter aortic valve implantation, Eur Heart J Cardiovasc Imaging. 2017 Jun 1;18(6):648-653.doi: 10.1093/ehjci/jex009.	
Medtronic Limited	Economic Report TAVI	015		**The rehospitalisation burden assumed in the NICE model might not properly reflect contemporary evidence however it is difficult to assess the methodology used given the lack of transparency.**	Thank you for your comment. Rehospitalisation transition probability in the first year comes from a weighted average of all the studies

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	and Economic Model TAVI			The NICE economic model assumes a rehospitalisation rate of 12.1% per year for SAVR, and a hazard ration (HR) of 1.24 for TAVI vs. SAVR. Unlike many of the other model assumptions that are clearly shown in the forest plots available in Evidence Review H, we were unable to see how these values were calculated and would appreciate more transparency on this. There does not appear to be any reference to the HR of 1.24 in the TAVI Economic Analysis Report. While the 12.1% might be reflective of the first year, rehospitalizations in subsequent rates appear to occur at a lower rate (for example, PARTNER 1 (Mack, 2015) showed rehospitalization rates at one year for SAVR and TAVI of 17.7% and 18.5%, and of 34.2% and 42.3% at five years (with no significant difference). In turn, this suggests an annual event rate in years 2, 3, 4, and 5 of approx. 4-5%. Furthermore, evidence of more recent trials suggests a lower burden of rehospitalizations altogether. For example, in the SURTAVI trial, aortic valve-related rehospitalizations at two years were 9.5% and 12.8% for SAVR and TAVI (no significant difference), suggesting around 5-6% annual events. In more recent low risk trials, PARTNER 3 (Leon, 2021) showed 12.5% and 8.5% rehospitalizations for SAVR and TAVI at two years, again suggesting 4-6% annual event rate. Further, the difference between TAVI and SAVR was significant ($p<0.05$), and importantly TAVI had a lower reintervention rate than SAVR (0.68 instead of the current assumption of 1.24 in the NICE model).	which gives a probability of 9% using the new meta-analysis (including only trials on 2nd and 3rd generation We recognized that this percentage does not reflect hospitalisation beyond the first year, so a new transition probability was calculated for the second year using trials with a longer follow-up. This results in a transition probability of 3% which is in line with the figure you reported. Regarding the RR, the committee have now agreed to use in the base case the treatment effects coming from trials evaluating only new generation valves which give a RR of TAVI vs SAVR of 0.73 in the first year and 1.91 in the years beyond. Data from PARTNER 3 and Evolut are included in this meta-analysis and were used to calculate the relative risk of reintervention.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We suggest NICE re-evaluate the underlying assumptions in the model with regard to annual baseline incidence and also regarding the RR of TAVI vs. SAVR reintervention to possibly increase the accuracy of resulting cost accounting in the model.	We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Economic Report TAVI Economic Model TAVI	016		**[This text was identified as confidential and has been removed].**	Thank you for your comment and for sharing the results of your analysis. The committee has discussed the opportunity of including this analysis in the model but recognized that it would be difficult to justify the use of unpublished and non-randomized data. The fact that the age gap between TAVI and SAVR patients is so large raises the concern that some of the outcomes may be influenced by this rather than the risk or the type of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					intervention. The committee decided to use data from UK TAVI trial (low risk) that has been scaled up for higher risks using the study on predictors of hospital resources by Reinhoul (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/). UK TAVI trial reports that median length of hospital stay and ICU stay after TAVI are, respectively, 0 and 3 days, whereas they are 1 and 8 days after SAVR. The analysis you provided suggests that Length of hospital stay and ICU stay follow a clear trend in SAVR patients, increasing along with the risk, whereas this is less evident in TAVI patients. We made sure that this pattern is fully captured in the model by scaling Length of hospital stay and ICU stay in SAVR using a higher scaling factor based on the analysis from Reiinhoul. TAVI ICU was set to 0 for all risk groups.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td>Medtronic Limited</td><td>Economic Report TAVI

and Economic Model TAVI</td><td>018
019
014
&
015</td><td>008
-
023
001
-
014</td><td>Medtronic believe implementation of survival projections in the current economic model are not sufficiently reflective of available evidence and might lead to underestimation of TAVI survival benefit.

Further to earlier comments about the Martin et al, 2017 study and the limitations of its use, Medtronic have concern about several aspects of the implementation of the survival projections in the model that might contribute to inaccuracies in calculation of QALY gains.

First, calibration of TAVI mortality is set to match relative overall survival at year 3 (to the standard population) from Martin 2017. Subsequently, SAVR mortality is calibrated relative to TAVI at year 1. It is unclear why 3-year TAVI survival is an important time point, but 1-year SAVR/TAVI relative survival is the other important time point. Often for other cost-effectiveness models, calibration will involve fitting several points along curves, not just one time point.

Further, the calibration (at 3 years) does not take into account intermediate vs. high-risk. In other words, while periprocedural mortality is modelled based on the specific risk level, the 3-year mortality used for calibration appears to be exactly the same value for high risk and intermediate risk, which leads to projections that are not reflective of trial-observed survival for the different risk strata (intermediate risk can be expected to have higher survival proportion at three years compared to high risk).

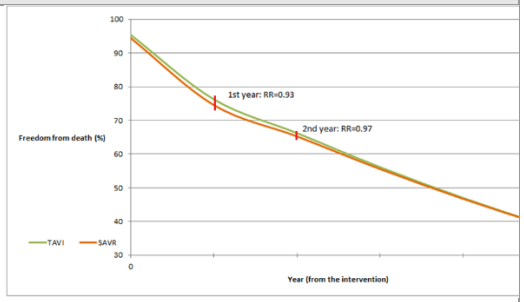
Also, the way the model is set up (TAVI survival being calibrated first, then SAVR survival calibrated next) leads to the following dynamic: If TAVI has</td><td>Thank you for your comment.

TAVI mortality was calibrated at the third year to reflect the mortality of Martin 2017, which was considered the best available evidence in the UK by the committee. The third year was chosen as it is the last follow-up of the study from Martin and colleagues. The calibration ensured that the mortality estimated in the model matches the one observed in Martin:

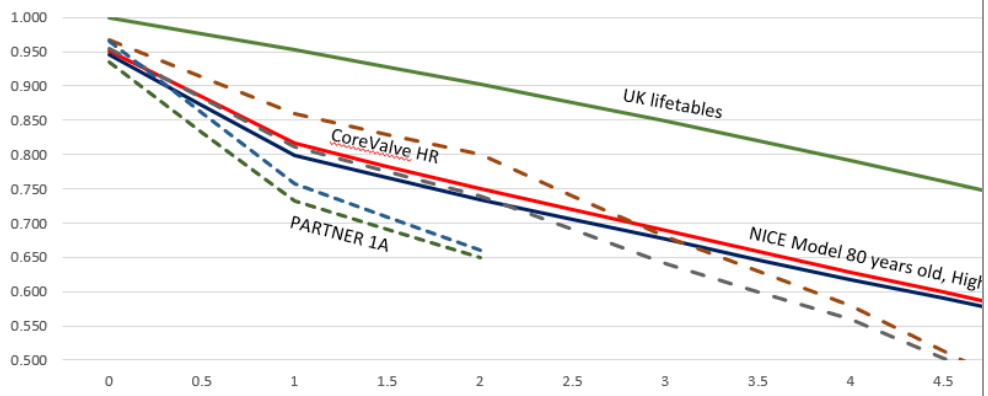
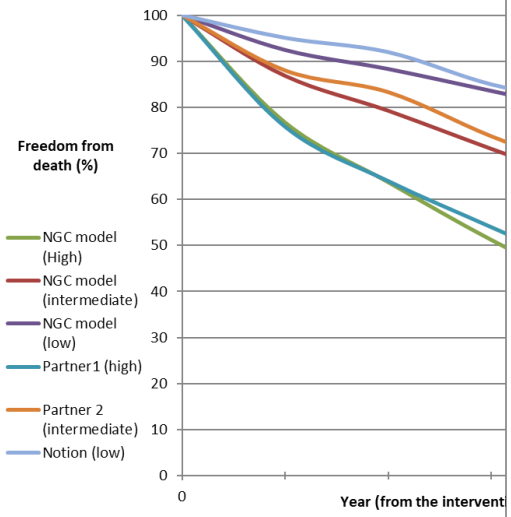
Survival
<table>
<tr><th>Year</th><th>Martin 2017 relative survival multiplied by lifetables</th><th>Model (intermediate risk)</th></tr>
<tr><td>1</td><td>86.82</td><td>85.72</td></tr>
<tr><td>2</td><td>79.25</td><td>78.63</td></tr>
<tr><td>3</td><td>70.97</td><td>71.00</td></tr>
<tr><td>4</td><td>62.97</td><td>63.66</td></tr>
<tr><td>5</td><td>55.33</td><td>56.64</td></tr>
</table>
</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				higher survival, then SAVR will also have higher survival (since the SAVR mortality rates are relative to the TAVI mortality rates). So, if the TAVI relative survival numbers were increased to reflect more recent data, the absolute difference in mortality between TAVI and SAVR would shrink (since the parameterisation assumes SAVR mortality is relative to TAVI mortality). This leads to an effect that would underestimate the benefit of TAVI. We are mindful of the challenge of survival modelling, but suggest NICE consider opportunities to structure the model in a way that the improvements in TAVI mortality would translate into not only better survival for TAVI, but importantly also an increased absolute difference in mortality between TAVI and SAVR. If this cannot be accomplished, incremental QALY calculations will be biased and run the risk of providing inaccurate projections of the TAVI vs. SAVR QALY gain that in turn might result in misleading ICER estimates. For year 3 and beyond, the model projects mortality for TAVI to be a linear prediction of the cumulative excess hazard between years 2 and 3. With limited data, this seems to be a reasonable assumption. However, the effects of this assumption should ideally be investigated in sensitivity analysis. It is not clear varying long-term mortality was part of conducted sensitivity analyses. The approach of calibrating survival at year 3 leads to survival curves that are defined by that point and through the assumed periprocedural mortality. The curves' shape in the period in-between these data points is driven by the calibration algorithm. The resulting curves are hence not informed by trial evidence (which is available for most RCTs for this period), and as	SAVR mortality is now calibrated at two points in time in the current version of the model to align the model to the trials follow-up data (at 1 and 2 years). Data show an important mortality improvement with TAVI after 1 year (0.93) which seems to decrease in the second year (0.97). To captured this in the model, we are calibrating 2 times: in the first cycle to make the 1-year RR equal to 0.93 and in the second cycle to make the 2-years RR equal to 0.97. This approach ensures that the mortality estimated by the model is reflecting available evidence, which are indicating survival benefits in the short term but not in the long term, where the survival curves converge (see Figure 1): Figure 1: 5-year survival SAVR vs TAVI predicted by the model (high risk)

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				such, calculated life years and QALYs can be expected to deviate somewhat from those that would have been calculated from a more refined along-the-trial assessment. Specifically, this not only relates to the individual shapes of the curves, but importantly to the "area between the curves", as this is the metric that defines survival benefit. As is shown from the graph below, the very narrow gap between the curves in the NICE model projection (shown here for 80 years old, high risk) is much narrower than the actual data observed in the CoreValve HR trial, and at least somewhat narrower than the PARTNER 1A trial (difference between TAVI and SAVR at one and two years: 1.8% and 1.6% in th eNICe model, as compared to 4.8% and 6.0% observed at these time points in the CoreValve HR trial). As a result, LY gain and in consequence, QALY gain, will be underestimated in the NICE model. The small difference between the curves in these initial years also has consequence for the long-term build-up of additional QALYs beyond three years, amplifying the effect of underestimated benefit. This effect is also visible when comparing the lifetime QALY gain for 80-year-olds at High Risk in the NICE model to those of prior High Risk cost-effectiveness models based on the CoreValve HR trial. While the NICE model projects 0.121 QALYs over the lifetime, compared to the findings in Reynolds et al. 2016 (0.32 QALYs) and Geisler et al, 2017 (0.41 QALYs). Both of these studies modelled detailed survival observed in the trial, followed by long-term survival projection. Part of the differences in	 We are now using different mortality rates for low, intermediate, and high-risk patients, meaning that the calibration at 3 years now takes into account the risk. This was achieved by applying confounder-adjusted hazard ratios to the mortality estimated in Martin 2017 for the other surgical risk groups. The resulting survival curves estimated from the model seem to compare well with trials with long follow-up (see Figure 2):

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

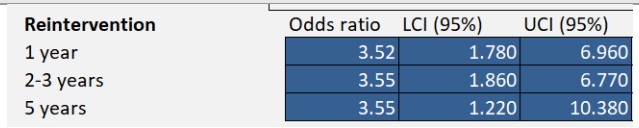
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				projected QALYs between the Reynolds and Geisler analyses are based on different underlying lifetables (US vs. Netherlands) and discount rates. It is important to note that the projected QALY gain is around three times higher than the QALY gain in the NICE analysis. In turn, this means that the NICE-calculated ICER is dramatically higher than an ICER that would be obtained based on the higher projected QALY gains. 	Figure 2  TAVI mortality is being used in the model as the baseline mortality against which SAVR mortality is calculated using the treatment effects at 1 and 2 years found in the trials. So we calibrate TAVI mortality first and then SAVR mortality (using the pooled risk ratio).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The committee decided to use the extrapolation based on Martin 2017 instead of trial-based data as they thought that a real-world UK source based on TAVI registry is more appropriate for an NHS-based economic analysis. In addition, mortality in the model is calculated using ONS lifetables which is consistent with Martin 2017, which used this data to estimate the denominator for the relative survival rates. The calibration, as mentioned before, ensures that the mortality estimated by the model is identical to Martin 2017 and therefore it is accurately reflecting the evidence. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Economic Report TAVI and Economic Model TAVI	021 023	023 004	**The use of Ler 2020 to model TAVI reintervention rates is flawed and non-representative of TAVI patient outcomes**. Medtronic acknowledge that reintervention data beyond 7 years is limited for TAVI however we have reviewed the Ler et al., 2020 and have found factual errors within the study which are being pulled into the economic model, subsequently overestimating the lifetime reintervention rates for TAVI and impacting the resultant ICERs. In alignment with our own assessment, Evidence Review H/8, Appendix I states that Ler et al., 2020 was excluded from the clinical assessment on the grounds that 'methods are not adequate/unclear'. It seems contradictory that this same paper would then be used as the sole data source to make impactful assumptions within the economic model. The NICE model applies the following odds ratios for TAVI vs. SAVR reintervention rates:	Thank you for your comment. Ler 2020 was excluded from clinical assessment because it did not use the Grade system required for the inclusion of literature reviews but it was initially included in the model as it was considered the most recent evidence on reintervention rates after TAVI. The committee has now decided that the evidence is not suitable as it was mostly focused on old generation valves. As it is clear that old generation valves are not used in the UK anymore and historically presented a higher rate of reinterventions than new generation valves, relative

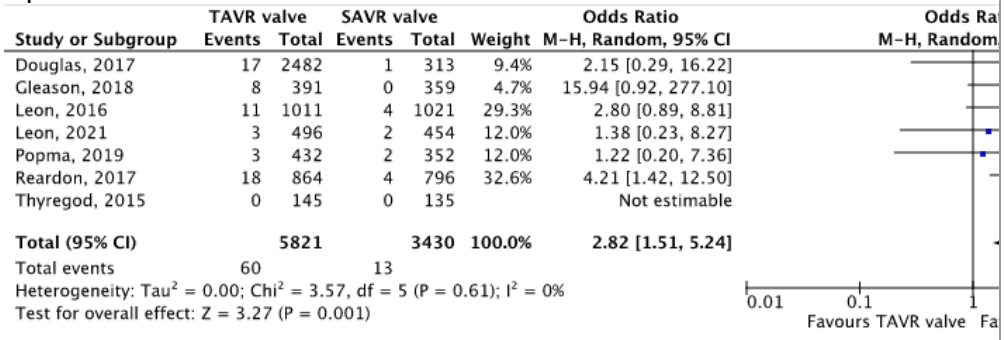
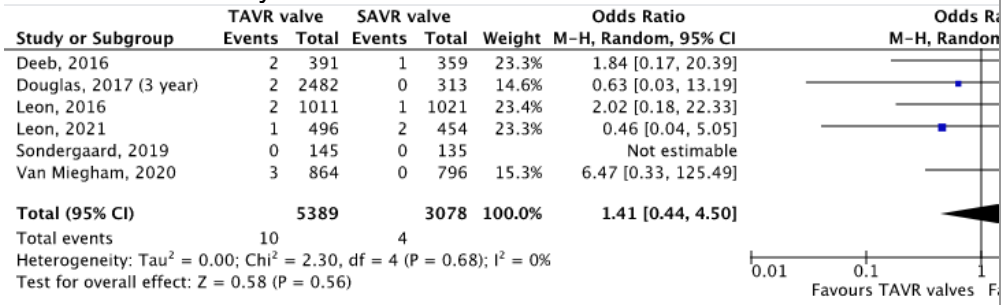
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

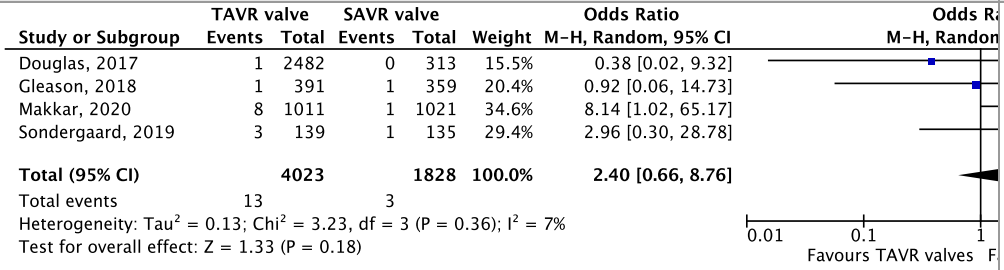
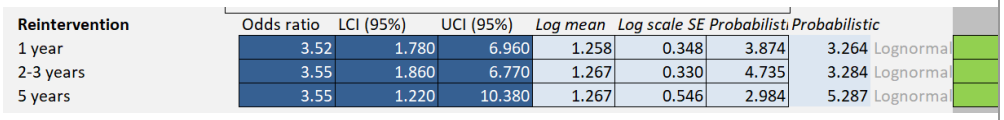
Stakeholder	Document	Page No	Line No	Comments	Developer's response
					treatment effects (including reintervention) in the base case scenario now come only from second and third generation valve trials (PARTNER 2, PARTNER 3, Evolut). This gives a relative risk for reintervention of 2.28 (TAVI vs SAVR) which is in line with the results of the Medtronic meta-analysis. As the treatment effect is now calculated using a meta-analysis of 3 studies only, we were not able to use time-dependent odds ratio but, as most of the reinterventions tend to occur either in the first year or many years after the first procedure, we think this will not affect the model significantly. For instance, your meta-analysis seems to suggest that the relative treatment effect is high during the first year, relatively low between year 1 and year 3, and then high again beyond the third year. The model predicts an extremely low number of reinterventions occurring between year 1 and 3 and, therefore, we do not expect that using different relative

When considering reinterventions, it is – first – important to note that many TAVI reinterventions occur due to moderate/severe PVL and often not due to structural valve deterioration (Makkar 2020, Pibarot 2020, Holy 2018). Nevertheless, the model appears to assume that all reinterventions are due to SVD. PVL is usually picked up immediately post-TAVI, resulting in higher reintervention rates at 1 year compared to subsequent years. The forest plots in Ler 2020 analyse the cumulative reintervention rates at 1, 2/3 and 5 years as reported in the trials meaning that many of the reinterventions that happened at 1 year are being double-counted at the 2/3-year and 5-year timeframes; hence why the odds ratios barely change as stated on page 21 in the economic report. Further, Ler et al double-counted the CoreValve High Risk trial in their 1-year forest plot since Adams 2014 and Gleason 2018 are two publications reporting on the same trial.

To correct the identified issues, we strongly recommend that the economic model uses time-dependent odds ratios for TAVI vs SAVR reintervention (up to 1 year, between 1 and 2/3 years, between 2/3 and 5 years) which we have calculated in the revised forest plots below. These updated plots not only correct the double-counting in Ler et al 2020, but also include Van Mieghem 2020, Popma 2019, Leon 2021 and Sondergaard 2019 to reflect all published RCT evidence.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Up to 1 Year:  Between 1 and 2/3 years  Between 2/3 years and 5 Years:	treatment effects in the first few years would significantly affect the results. Some headings in the consultation version of the model workbook were misleading: the model did not assume that all reinterventions are caused by SVD. The source used for baseline reintervention risk after SAVR (Rodriguez-Gabella) captures all the reinterventions occurring in a cohort of surgery patients for a period of13 years. Likewise, the relative treatment effect used to estimate reintervention rates in the TAVI cohort was calculated looking at reintervention events occurring in the two arms of the trials regardless of whether the reinterventions are caused by PVL or SVD. As Medtronic pointed out, recent evidence on new generation valves (SAPIEN 3 and Evolut) seem to suggest that rates of reintervention after SAVR and TAVI will become similar in the future, especially if third

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 Replacing the cumulative odds ratios with the time-dependent ones outlined above, and shown highlighted in green below, reduces incremental costs and increases incremental QALYs and therefore lowers the ICER; for example the ICER for High Risk patients at 80 years old reduces by more than £10,000/QALY.  In this context, it is again important to note here that the earlier RCTs used previous iterations of TAVI valves and changes have been made to the valves to improve hemodynamic performance, reduce reintervention rates and likely improve valve durability, although longer term data is required to confirm durability. As shown in the 5-year forest plot, the Makkar 2020 (PARTNER 2A trial using the SAPIEN XT Valve) results are heavily influencing the odds ratio with a weighting of 34.6% and individual OR = 8.14. Reinterventions after	generation valves continue to replace older models. We have added therefore a scenario analysis where relative treatment effect is almost equal to 1 (1.08) reflecting the findings of PARTNER 3 and Evolut trials only (Sapien 3 and Evolut valves). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

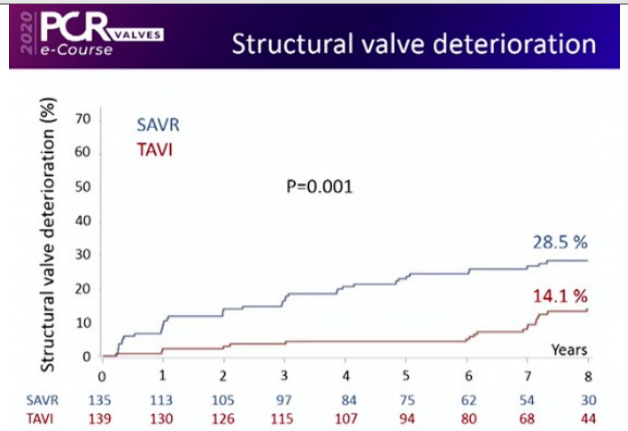
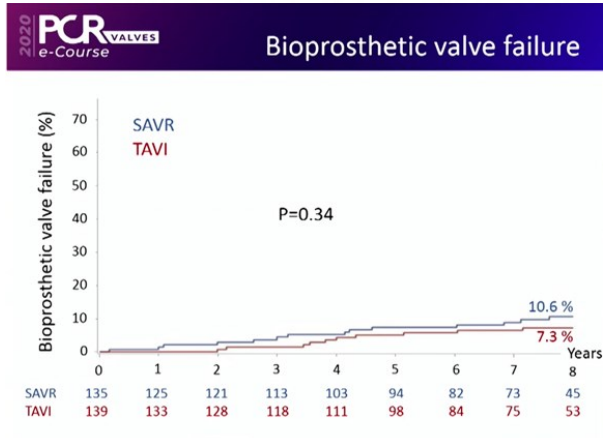
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				TAVR (3.2% at 5 years) were due to aortic regurgitation (11 of 21 cases) or progressive stenosis (10 of 21 cases) and most patients were treated with repeat TAVR or Balloon Aortic Valvuloplasty (BAV). Also of note, in-hospital mortality from valve reintervention was 5% (1 of 21 patients) in the TAVR group and 50% (3 of 6 patients) in the surgery group. Pibarot 2020 is an example of a study that may help to provide evidence regarding durability of the newer generation TAVI valves. The study concluded that compared with SAVR, the third-generation SAPIEN 3 has a rate of SVD that was not statistically different from SAVR. With SAPIEN XT, the vast majority of bioprosthetic valve failures (BVFs) and valve reinterventions were related to SVD, whereas in the SAPIEN 3, most BVFs were related to nonstructural dysfunction (i.e., paravalvular aortic regurgitation). As outlined above, PVL is often the cause of post-TAVI reintervention rather than SVD or BVF and in fact, many RCTs have shown higher rates of SVD in SAVR compared to TAVI. In the CoreValve High Risk trial through 5 years, fewer TAVI patients had moderate SVD versus SAVR (9.2% vs. 26.6%, p<0.001) or severe SVD (0.8% vs. 1.7%, p<0.001) yet freedom from valve reintervention was 97.0% for TAVI and 98.9% for SAVR (p=0.04) (Gleason 2018)*. The 8-year data from the NOTION trial was recently presented at PCR-valves e-Course 2020. BVF for surgical bioprostheses has previously been defined as re-intervention, with a risk of under-estimating the incidence of SVD as some patients will not undergo re-intervention due to high age, co-morbidity burden or frailty. Sondergaard et al therefore evaluated durability	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				using standardised definitions of bioprosthetic valve deterioration. The risk of structural valve deterioration was lower for TAVI versus SAVR (14.1% versus 28.5%; p=0.001), whereas the risk of bioprosthetic valve failure was similar (7.3% versus 10.6%; p=0.34) after eight years of follow-up (presented by Sondergaard, 2020). We understand that NICE need to model reinterventions in this instance, but we hope that these data, although not yet published in a peer-reviewed journal, can help to demonstrate that equal long-term BVF rates, and therefore equal reintervention rates beyond 5 years for TAVI vs. SAVR is realistic. Therefore, we support the used of this assumption for sensitivity analysis.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				When data was pooled from the CoreValve/Evolut RCTs and associated continued access studies (CoreValve US Pivotal Extreme-Risk trial and CAS, CoreValve US Pivotal High-Risk trial and CAS, SURTAVI and SURTAVI CAS and Evolut Low Risk Trial), we can see that PVL was by far the most common reason for reintervention (64% of reinterventions) and we see that 83.9% of all reinterventions successfully resolved the causative event (Durability from the CoreValve IDE Studies, Kendra J. Grubb, MD, MHA, Emory University, Atlanta, GA, Presented at CRT Virtual 2021 – manuscript in progress):	

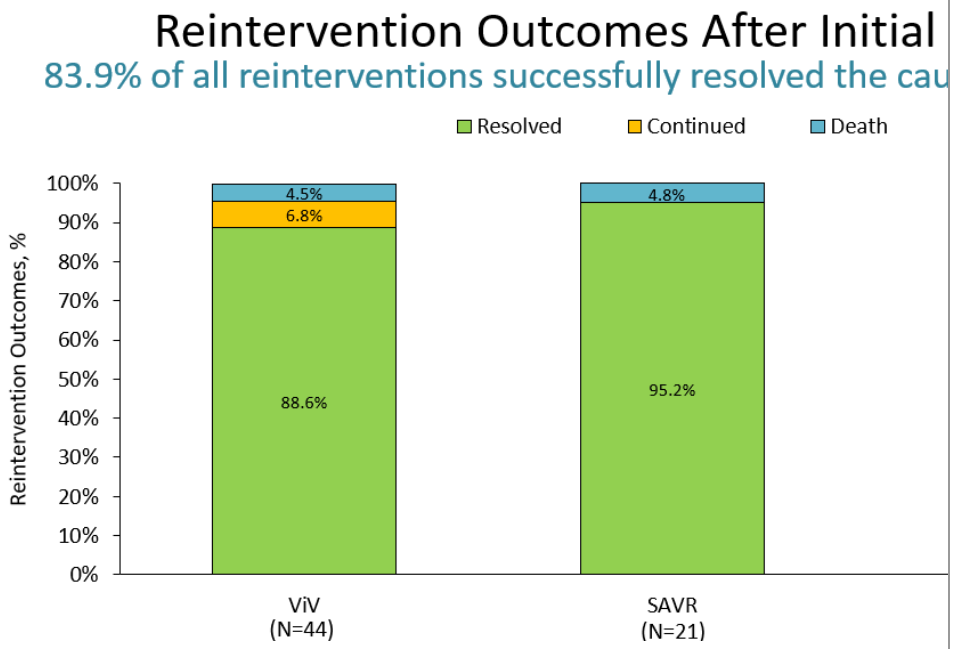
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response

Reasons for Reintervention

	PVL	Central AR	Aortic Stenosis	Endocarditis
TAVR (N=88)	**n=56**	**n=7**	**n=3**	**n=7**
Early (0–1 year)				
Percutaneous	35	5	1	0
Surgical	6	2		3
Late (>1–5 years)				
Percutaneous	13	0	1	0
Surgical	2	0	1	4
SAVR (N=18)	**n=4**	**n=1**	**n=5**	**n=7**
Early (0–1 year)				
Percutaneous	1	0	0	0
Surgical	1	0	0	2
Late (>1–5 years)				
Percutaneous	1	1	4	0
Surgical	1	0	1	5

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 *Please note different trials may use different definitions of Structural Valve Deterioration (SVD) and those used in Gleason 2018 are likely to overexaggerate the rate of SVD in comparison to the more contemporary definitions, for example those used in the recently presented NOTION data. **REFERENCES:**	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Søndergaard L, Popma JJ, Reardon MJ, Van Mieghem NM, Deeb GM, Kodali S, et al. Comparison of a Complete Percutaneous versus Surgical Approach to Aortic Valve Replacement and Revascularization in Patients at Intermediate Surgical Risk: Results from the Randomized SURTAVI Trial. Circulation. 2019 • Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. New England Journal of Medicine. 2019;380(18):1706-15. • Van Mieghem NM, Popma JJ, Deeb GM, Yakubov SJ, Serruys PW, Windecker S, et al. Complete 2-Year Results Confirm Bayesian Analysis of the SURTAVI Trial. JACC: Cardiovascular Interventions. 2020;13(3):323-31. • Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement. New England Journal of Medicine. 2020;382(9):799-809. • Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. Journal of the American College of Cardiology. 2018;72(22):2687-96 • Grubb K J, Durability from the CoreValve IDE Studies, Kendra J. Grubb, MD, MHA, Emory University, Atlanta, GA, Presented at CRT Virtual 2021 – manuscript in progress • Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Intermediate-Risk Patients. New England Journal of Medicine. 2016;374(17):1609-20 • Douglas PS; Leon MB; Mack MJ; Svensson LG; Webb JG; Hahn RT; Pibarot P; Weissman NJ; Miller DC; Kapadia S; Herrmann HC; Kodali SK; Makkar RR; Thourani VH; Lerakis S; Lowry AM; Rajeswaran J; Finn MT; Alu MC; Smith CR; Blackstone EH; Longitudinal Hemodynamics of Transcatheter and Surgical Aortic Valves in the PARTNER Trial. JAMA cardiology Vol. 2 (11), pp. 1197-1206; Publisher: American Medical Association; PMID: 28973520. 2016 • Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine. 2017;376(14):1321-31. • Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. Journal of the American College of Cardiology. 2015;65(20):2184-94. • Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, et al. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. Journal of the American College of Cardiology. 2016;67(22):2565-74. • Leon, M. B. et al. (2021) 'Outcomes 2 Years After Transcatheter Aortic Valve Replacement in Patients at Low Surgical Risk', Journal of the American College of Cardiology. Elsevier Inc., 77(9), pp. 1149–1161. doi: 10.1016/j.jacc.2020.12.052.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Ler A, Ying YJ, Sazzad F, Choong A, Kofidis T. Structural durability of early generation Transcatheter aortic valve replacement valves compared with surgical aortic valve replacement valves in heart valve surgery: a systematic review and meta34 analysis. Journal of Cardiothoracic Surgery. 2020; 15(1):127 • Pibarot P, Ternacle J, Jaber WA, Salaun E, Dahou A, Asch FM, et al. Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. Journal of the American College of Cardiology. 2020;76(16):1830-43 Holy EW, Kebernik J, Abdelghani M, et al. Long-term durability and hemodynamic performance of a self-expanding transcatheter heart valve beyond 5 years after implantation: A prospective observational study applying the standardized definitions of structural deterioration and valve failure. EuroIntervention 2018; doi:10.4244/EIJ-D-18-00041.	
Medtronic Limited	Economic Report TAVI Economic Model TAVI	024	018 - 023	**The assumption that all reintervention patients return to baseline QALYs for 1 year prior to their reintervention is overestimating the disutility.** The model assumes that people with SVD requiring a reintervention would show symptoms comparable to patients who have not received an intervention yet. Therefore, their utility score during the year prior the reintervention is expected to be equal to the utility score at baseline. Firstly, and as discussed in our previous comments related to reintervention above, it is important to note that the cause of reintervention is very often due to PVL and not related to SVD. This is well-documented, for example, Pibarot et al. 2020 report that 58% of TAVI reinterventions	Thank you for your comment. The committee discussed this aspect of the model. They agreed that people needing a reintervention would show some of the symptoms they had before the first intervention though it is unlikely that this would last for as much as a year, as they would probably be treated earlier. A decision was made to limit the time of the disutility prior to reintervention to 6 months, which was considered the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				were due to PVL, while 32% were SVD-related, and 5% each due to thrombosis and valve migration. We therefore believe that the current model assumption that all reinterventions are due to SVD is not reflective of reality. Further, the current model assumes that all patients return to baseline QoL for a full year prior to reintervention. We believe this is highly unlikely as symptomatic patients can be expected to be picked up and treated much quicker. Also, their quality of life, from a clinical perspective, is unlikely to return to baseline QoL for any prolonged period of time. In combination, the current assumptions seem to unduly reduce the projected QALY gains in the TAVI strategy. We would recommend that NICE seek input from a range of TAVI and SAVR implanters to validate this assumption. **REFERENCES:** • Pibarot P, Ternacle J, Jaber WA, Salaun E, Dahou A, Asch FM, et al. Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. Journal of the American College of Cardiology. 2020;76(16):1830-43	average time a patient would need to wait before undergoing a reintervention in the NHS. The model does not assume that all reinterventions are due to SVD, although we recognize that some headings in the consultation version of the model workbook were misleading. The source used for baseline reintervention risk after SAVR (Rodriguez-Gabella) captures all the reinterventions occurring in a cohort of surgery patients for a period of13 years. Likewise, the relative treatment effect used to estimate reintervention rates in the TAVI cohort was calculated looking at reintervention events occurring in the two arms of the trials regardless of whether they are caused by PVL or SVD.
Medtronic Limited	Economic Report TAVI	027	001 - 009	**Medtronic challenges the Currency Codes used to calculate the Index Procedural Costs for High Risk and Intermediate Risk patients.** The economic model uses National Reference costs to calculate the cost of SAVR and TAVI interventions without the hospital stay component. Aligned with the current NHS England Commissioning policy for TAVI from 2013,	Thank you for your comment. We disagree with the fact that only patients deemed unsuitable for surgery are offered TAVI in the UK. Martin 2017, which used data drawn

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	and Economic Model TAVI			only patients who are deemed unsuitable for surgery are offered TAVI. Therefore, reference cost data from 2017-18 for TAVI will be based upon this specific risk group of patients. Typical TAVI procedures are carried out via a transfemoral approach and as such the Currency Code **EY21A** is for patients with a CC score of 8+ and **EY21B** are for patients with a CC score of 0-7. Patients with a CC score of 7 could indeed still be classed as a high risk/inoperable patient due to their comorbidities and so it is inaccurate to class these as intermediate risk patients in the model, especially considering intermediate risk patients are not routinely commissioned in England. In contrast, the surgical aortic valve procedures would generally be performed on Lower Risk patient groups. These lower risk groups can be evidenced with the additional Currency Codes available for SAVR procedures, for example **ED25C, ED25B, ED25C** codes are for standard procedures with CC scores of 0-5, 6-10 & 11+ respectively. Complex SAVR procedures **ED24C, ED24B** and **ED24C** are for patients with CC scores of 0-5, 6-10 & 11+ respectively. Medtronic understand that patients who are deemed 'extreme surgical risk' are very unlikely to undergo a SAVR procedure and would either be offered TAVI or palliative care. Therefore, Medtronic strongly recommend that to obtain a direct comparison across interventional procedures, the cost for high risk SAVR patients should be taken from ***ED24A - Complex, Single Heart Valve Replacement or Repair, with CC Score 11+***	from the UK TAVI registry, reports an average STS of 5, suggesting that many intermediate and high-risk patients currently receive TAVI in the UK. We do recognize, though, that many extremely high-risk/inoperable patients are currently treated with TAVI and this may over-estimate the cost of TAVI derived from the NHS Reference Costs. Hence, it was decided to use the HRG EY21B referring to patients with CC score of 0-7 as this group is probably excluding extremely high/inoperable risk patients. This HRG was assigned to all TAVI patients (high, medium, and low risk) as suggested by Medtronic. Regarding SAVR, the committee agreed to continue stratifying the cost based on risk. We agree that very few people with extreme risk receive SAVR in the UK and that most of the procedures are performed on low-risk patients. CC score refer to the comorbidity of the patients so it seems

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				For Intermediate Risk groups Medtronic strongly recommend that a weighted average of ***ED24B - Complex, Single Heart Valve Replacement or Repair, with CC Score 6-10*** and ***ED24C - Complex, Single Heart Valve Replacement or Repair, with CC Score 0-5*** is used. Medtronic strongly refutes the use of ***EY21A - Transcatheter Aortic Valve Implantation (TAVI) using Transfemoral Approach, with CC Score 8+*** being considered in the economic model as it would only be assigned for extreme risk patients. Extreme risk patients are out of scope as per the economic plan published in January 2021. Therefore, Medtronic suggests that patients who are deemed high Risk would be assigned ***EY21B - Transcatheter Aortic Valve Implantation (TAVI) using Transfemoral Approach, with CC Score 0-7***. Intermediate Risk patients would not routinely undergo a TAVI procedure and so there is no accurate reference cost which can be assigned for this group and we acknowledge that an assumption needs to be made. Therefore, we recommend that for intermediate risk groups only EY21B is assigned to this group.	to be a reasonable proxy for surgical risk. Hence it was decided to take a weighted average of complex and standard procedure and assign them to each surgical risk category according to CC score: • CC score +11 -> high risk • CC score 6-10 -> intermediate risk • CC score 0-5 -> low risk Only conversion to reintervention, which was considered a major complication of TAVI, uses ED24A as it is likely associated with the highest cost reported. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Economic Report TAVI and Economic Model TAVI	027	012	**Medtronic feel that data used for ICU and Ward Length of Stay for TAVI patients is not consistent with current practice.** Within the economic model NICE employ ICU and ward Length of Stay (LoS) from RCT data. It is noted by NICE that this data is taken from a Non-UK setting. However, there is no consideration given to the procedural efficiency advancements of the TAVI procedure in recent years and employing ICU and LoS data from historical RCTs is not consistent with current clinical practice within the NHS. The Cardiology Get It Right First Time report (GIRFT) (2021) report recommends that for TAVI, 'uncomplicated patients should routinely be returned to a monitored ward bed after a short period of observation in a recovery area (one to two hours) rather than requiring a CCU admission. Most uncomplicated patients should be fit for discharge within 72 hours and maybe sooner, social circumstances permitting'. Medtronic acknowledge that the GIRFT report states that the average length of stay for TAVI is 11.4 days. However, it is important to note that this length of stay encompasses all TAVI procedures including both inoperable and non-elective patients who often have a long length of stay prior to their TAVI procedure. Non-elective patients highlight the broken NHS pathway because they should be	Thank you for your comment. The committee agreed that the figures for ICU and hospital LOS used in the consultation version of the model were not representative of the UK setting. It was agreed, therefore, to use the number of days collected in the UK TAVI trial as this better reflects current practice. These suggest that TAVI patients rarely need to spend a day in ICU and that the median length of hospital stay is 3 days in the low-risk group. We disagree that the NHS Reference Costs is not representative of the cost incurred by lower risk groups. Current practice is very heterogenous and many people at intermediate and lower risk receive TAVI in the UK, as shown in studies several based on the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				diagnosed much earlier, allowing them to be treated appropriately as an elective patient with TAVI or SAVR. This contemporary practice has indeed been subject to other publications which report same day discharges following a TAVI procedure as described by Rai (2021), M^{c}Calmont (2019) and Généreux (2016). • McCalmont, G. *et al.* (2019) '136 Same-day admission facilitated by a nurse led pathway reduces hospital length of stay for transfemoral transcatheter aortic valve implantation', in *Heart*. BMJ, p. A112.2-A112. doi: 10.1136/heartjnl-2019-bcs.133. • Rai, D. *et al.* (2021) 'Transcatheter aortic valve replacement same-day discharge for selected patients: a case series', *European Heart Journal - Case Reports*. Edited by F. Giannini et al. Oxford University Press (OUP), 5(2). doi: 10.1093/ehjcr/ytaa556. • Généreux, P., Demers, P. and Poulin, F. (2016) 'Same day discharge after transcatheter aortic valve replacement: Are we there yet?', *Catheterization and Cardiovascular Interventions*. John Wiley and Sons Inc., 87(5), pp. 980–982. doi: 10.1002/ccd.26059. We kindly request that NICE accepts that the RCT data used in the economic model is outdated and not consistent with current practice and consider approaching NHS providers to obtain data sets aligned with current practice. Further, although it was noted by NICE that because TAVI is currently available to High-Risk patients, the National Reference Costs is not representative of the costs incurred by lower risk groups.	UK TAVI registry (e. g. Martin 2017 with a mean STS around 5). We excluded HRG EY21A related to TAVI with a cc score higher than 8 as the committee thought it refers to people at high surgical risk or inoperable. EY21B, instead, was considered to reflect the cost of TAVI for lower risk groups. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				this data would be more representative of current practice if it were aligned to risk stratification for both TAVI and SAVR patients. **REFERENCES:** • GIRFT 2021: https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf	
Medtronic Limited	Economic Report TAVI and Economic Model TAVI	028	006	**Medtronic refutes the mechanism used to calculate the hospital ward stay costs. Deriving these costs from 'Excess Bed Days' we believe has enhanced the unit costs for TAVI and reduced those for SAVR, *£473* and £325 respectively.** We therefore kindly ask that NICE use a consistent assumption of £325 for the cost of one bed day for both a cardiac surgery ward and a cardiology ward as we cannot find a logical reason why there would be a difference.	Thank you for your comment. The committee has now decided to follow your suggestion and use the cost of £325 for both TAVI and SAVR. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medtronic Limited	Economic Report TAVI and Economic Model TAVI	029	010	**Medtronic do not recognise the price of the TAVI valve used in the cost-effectiveness model.** The price of £20,280 obtained from the NHS Supply Chain Catalogue is not consistent with the current prices charged for Medtronic TAVI valves including the associated devices used to implant the valve. As noted in the Guide to the methods of technology appraisal 2013, 5.5 Evidence on resource use and costs, page 45. 'Value added tax (VAT) should be excluded from all economic evaluations but included in calculation of the budgetary impact when the resources in question are liable for this tax'. Therefore, the prices detailed here are prices before VAT. 26The above prices are available to all NHS hospitals across the United Kingdom. The TAVI Valves and Delivery Systems to deploy these devices are listed in the category of High-Cost tariff excluded devices (HCTED), for which NHS England is the responsible commissioner. NHS England via NHS Supply Chain, delegates the procurement of these devices, via Category Tower 6, awarded to the Health Solutions Team (HST). The majority of Trusts within England procure these products via HST. For those Trusts that do not transact via HST the above prices are still available to them. **Medtronic asks that NICE consider obtaining more accurate total industry TAVI system costs directly from HST and the economic model is updated to reflect the actual cost of the TAVI valve system.**	Thank you for your comment. The price of £20,280 has now been removed from the revised version of the model as it was referring to only Lotus valve and not representative. Instead, the committee agreed to use in the base case scenario the price of £17,500 provided by the NHS Supply Chain. This is the average price across the volume for the period Y2020, P01, W01 (w/c 01-04-2019) to Y2020, P12, W53 (w/e 31-03-2020) (53 wks. data in total). This price reflects the actual average price at which the NHS is purchasing most of the valves in the UK (80% of all the valves purchased). A sensitivity analysis was conducted to see the implication for cost-effectiveness if the average price drops to £15,000. Furthermore, a threshold analysis was

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					conducted on the price of the valve for each surgical risk group. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Economic Report TAVI And Economic Model	030	017	**Using Reference Costs for adverse events within 30 days in the Decision Tree model results in double counting costs.** 30 Day adverse event costs for Major Bleeding, Vascular Complications and Pacemaker, were taken from 2018-19 Reference Costs. Medtronic contests the use of this data as these Currency Codes are for standalone index procedures.	Thank you for your comment. The committee agreed that most of the adverse event cost was already included in the NHS Reference Costs HRG. Therefore, it was decided to exclude the short-term costs of major bleeding, vascular complication and pacemaker implantation from the

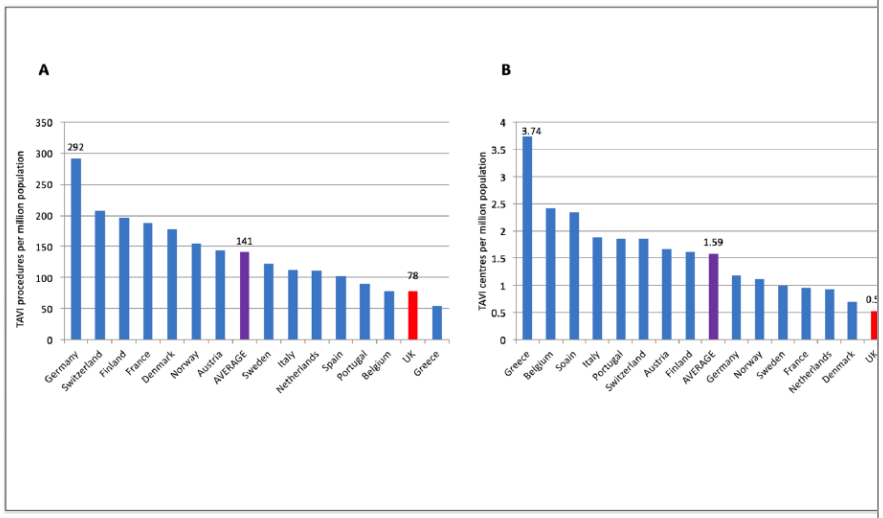
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	TAVI			Medtronic acknowledge that unpublished data cannot be used, however, to provide further evidence that NHS Reference Costs include adverse events during the procedure we wish to share data which Medtronic intend to publish in the near future. **[This text was identified as confidential and has been removed].** This data illustrates the actual cost of the procedure and that adverse events that occurred during an episode of care, specifically whilst undergoing a TAVI procedure, would indeed be captured within the EY21A or EY21B currencies which have a 2017-18 National Average Unit Cost of £7,681 and £6,006 respectively for TAVI. Consequently, including Currency Codes for Major Bleeding, Vascular Complications and Pacemaker in the Decision Tree model would result in double counting and therefore Medtronic recommends that adverse event costs are removed. It is also important to note here that there are other adverse events that NICE have not modelled as an added cost, for example Atrial Fibrillation which is considerably higher in SAVR patients as demonstrated in the RCTs. Whilst we support that the costs of AF are likely captured within the references costs for TAVI and SAVR, this raises the question why NICE felt that other acute costs (major vascular complications, major bleeds and pacemakers) should be considered outside of the reference costs during an episode of care.	decision tree model in the base case scenario. There was a bit of uncertainty regarding pacemaker implantation as some members of the committee stated that, in some cases at least, it occurs after the first hospitalisation and, therefore, would incur the cost of an additional stay. A sensitivity analysis was conducted where all the adverse event costs are separately accounted for as in the consultation version of the model. This did not change the results of the model. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Economic Report	045	008 - 010	**We recommend that NICE reconsider the following statement: "This price is not too distant from the price TAVI is currently purchased in other developed countries as France or Germany".** We feel this comment is somewhat inaccurate and should be supported by publicly available references to provide context. Both Germany and France have much higher TAVI rate per million population in comparison to the UK as demonstrated by the figure below (Ali 2021).	Thank you for your comment. The revised model, which was accepted by the committee found, in its current state, indeed a different price in the threshold analysis not that dissimilar to the price TAVI valves are purchased in other countries. We recognized that TAVI in other European countries like Germany is purchased at a higher volume, but a NICE health economics analysis must be based on the price TAVI is currently purchased in the NHS to inform. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				 **Figure 1** (A) Comparison of number of TAVI procedures carried out per million population in different European Comparison of number of TAVI centres per million population in different European countries. TAVI, transcatheter implantation. A recent society consensus statement recommended that all patients above 75 years old should be treated with TAVI if appropriate, along with a heart team decision regarding TAVI or SAVR for patients between 70 and 75 (Kuch et al., 2020). An implant rate of 292 per million equates to 24,200 TAVI patients per year in Germany, over 4 times higher than the UK. In the context of pricing, this higher volume can be expected to have contributed to lower prices being reported for Germany.	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				In France, TAVI is performed at a rate of 188 per million, again much higher than the rate in the UK. The reimbursement system in France requires the valve companies to submit dossiers for each new indication and a reimbursement price for each valve is defined separately. All reimbursement prices are available online and do not appear to be at the level stated on page 45 of the Economic Report. For example, the Medtronic CoreValve Evolut (R and PRO) is listed at €15,419.21 (https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000038962119). Medtronic TAVI valves are reimbursed across extreme, high and intermediate risk cohorts and the French authorities are also in the process of reviewing Medtronic CoreValve Evolut R and PRO for reimbursement in low risk patients. The clinical evaluation for this assessment can be found here and the economic assessments are currently in progress: • CoreValve Evolut R (cf p23 for the target population) : https://www.has-sante.fr/jcms/p_3238888/fr/corevalve-evolut-r • CoreValve Evolut PRO (cf p 22 for the target population) : https://www.has-sante.fr/jcms/p_3238891/fr/corevalve-evolut-pro Finally, the price referencing of Germany and France, in relation to a price threshold analysis, disregards the errors in the model as described in our comments. If a revised basecase is accepted by the Committee, this would significantly change the resultant ICERs and would therefore require revision of this narrative. **REFERENCES:**	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Ali N, Faour A, Rawlins J, et al. 'Valve for Life': tackling the deficit in transcatheter treatment of heart valve disease in the UK. Open Heart 2021;8:e001547. doi:10.1136/openhrt-2020-001547 • Kuck, K., Bleiziffer, S., Eggebrecht, H. et al. Konsensuspapier der Deutschen Gesellschaft für Kardiologie (DGK) und der Deutschen Gesellschaft für Thorax-, Herz- und Gefäßchirurgie (DGTHG) zur kathetergestützten Aortenklappenimplantation (TAVI) 2020. Kardiologe 14, 182–204 (2020)	
Medtronic Limited	Economic Report TAVI and Economic Model TAVI	047 014	001 - 007	**The use of Rodriguez-Gabella 2018 to model the baseline SAVR reintervention rates up to 13 years is likely to overestimate the number of SAVR reinterventions which in turn impacts the number of TAVI reinterventions and therefore the ICER** The model assumptions for baseline SAVR reintervention rates up to 13 years (and subsequent linear extrapolation) relies on a single paper, Rodriguez-Gabella 2018 which we feel is inappropriate given the impact that uncertainties can have on the resultant ICER. Rodriguez-Gabella was a single-centre retrospective study of 985 patients who underwent SAVR between 2002 and 2004. A mixture of prosthesis types were used including 7.1% Mitroflow valve which has since been removed from the market following a 2017 device alert (MHRA 2017) and multiple studies highlighting durability concerns. We understand that LivaNova have since replaced Mitroflow with a new valve, Crown PRT, which has a phospholipid reduction treatment designed to improve durability (https://www.livanova.com/en-GB/Home/Heart-Valves/Aortic-Heart-Valves.aspx). Rodriguez-Gabella et al., 2018 observed that the Mitroflow	Thank you for your comment. The paper from Rodriguez-Gabella was chosen as it has the longest follow up. Since, the rate of reintervention increases significantly over time the length of follow-up is crucial. Using other data would have involved relying more on extrapolation. Regarding the rates predicted in Rodriguez-Gabella, we do not think that they overestimate reintervention rates in the UK. At year 1, the rate predicted with the model is 1.4% which is comparable with the 30-days risk of reintervention after SAVR

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>valves were associated with an increased risk for SVD, and most (>80%) patients with clinically relevant SVD had a reintervention. This indicates that a significant proportion of the reinterventions will have been in patients with Mitroflow and thus indicates that the baseline probabilities of SAVR reintervention are likely over-estimated, with resultant effect also for the OR-derived TAVI estimate. It is also worth noting that the average age of patients in the Rodriguez-Gabella study was 72 which is younger than most high-risk patients and we know that reintervention is heavily dependent on age of the patient at implant.

The 5-year SAVR reintervention rates reported in the RCT data also help to demonstrate that the current model appears to overestimate the baseline SAVR reintervention rates:

<table>
<tr><th>Markov Cycle</th><th>MODEL Reintervention rate (Rodriguez-Gabella 2018)</th><th>PARTNER 2 SAVR Reintervention at 5 Years (Makkar 2020)</th><th>CoreValve High Risk SAVR Reintervention at 5 Years (Gleason 2018)</th><th>NOTION SAVR Reintervention at 5 Years (Sondergaard 2019)</th><th>P
Rei
(Dc</th></tr>
<tr><td>5</td><td>1.99%</td><td>0.8%</td><td>1.1%</td><td>0.7%</td><td></td></tr>
</table>

REFERENCES:
• Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, et al. Five-Year Outcomes of Transcatheter or Surgical Aortic-</td><td>found in the UK TAVI trial (1.6%) and lower than the 1-year risk (2.9). UK TAVI trial is a recent trial which should reflect the effectiveness of biological valves currently used in the UK.</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Valve Replacement. New England Journal of Medicine. 2020;382(9):799-809. • Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. Journal of the American College of Cardiology. 2018;72(22):2687-96 • Søndergaard L, Popma JJ, Reardon MJ, Van Mieghem NM, Deeb GM, Kodali S, et al. Comparison of a Complete Percutaneous versus Surgical Approach to Aortic Valve Replacement and Revascularization in Patients at Intermediate Surgical Risk: Results from the Randomized SURTAVI Trial. Circulation. 2019 • Douglas PS; Leon MB; Mack MJ; Svensson LG; Webb JG; Hahn RT; Pibarot P; Weissman NJ; Miller DC; Kapadia S; Herrmann HC; Kodali SK; Makkar RR; Thourani VH; Lerakis S; Lowry AM; Rajeswaran J; Finn MT; Alu MC; Smith CR; Blackstone EH; Longitudinal Hemodynamics of Transcatheter and Surgical Aortic Valves in the PARTNER Trial. JAMA cardiology Vol. 2 (11), pp. 1197-1206; Publisher: American Medical Association; PMID: 28973520. 2016 • MHRA 2017: https://www.gov.uk/drug-device-alerts/biological-replacement-pericardial-aortic-heart-valve-mitroflow-lx-sizes-19mm-and-21mm-risk-of-early-structural-valve-deterioration	
Medtronic Limited	Economic Report TAVI	033	001	**NICE overestimate the unit cost of pacemaker implantation in the economic model by including the cost of biventricular pacemaker implantation within the unit cost.**	Thank you for your comment. The committee agreed to now assume in the base case analysis that all 30-day adverse event costs are included

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	and Economic Model TAVI			In previous consultation comments within our response, Medtronic have recommended that NICE assume all 30-day AE costs are included in the reference costs. However, should NICE opt to reject this recommendation, we disagree with Biventricular Pacemakers being included in the weighted averages for the Cost of a Pacemaker. Medtronic understands that Biventricular pacemakers are implanted when the right atrium and right and left ventricles require pacing. Evidence does not suggest that TAVI induces heart failure and if these devices are being implanted following a TAVI procedure then this is most likely indicated for a comorbidity which is unrelated to TAVI or is unwittingly being over prescribed. Medtronic recommends that the weighted average is recalculated to exclude Biventricular Pacemakers and the economic inputs in the model adjusted accordingly.	in the reference costs. There is a sensitivity analysis where each AE is costed as a separate episode (in this one Biventricular Pacemaker are excluded). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Evidence Review H	549	All	**Medtronic do not feel it is appropriate to use an excluded health economic study (Fairbairn 2013) as reasoning for exclusion of several other health economic studies.**	Thank you for your comment. After a further review of Fairbairn 2013, we ultimately decided to include this study as the authors conducted a threshold analysis on the price of the

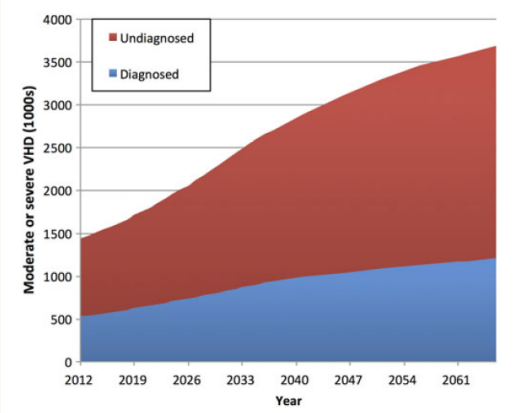
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Evidence Review H, page 549, Appendix I.22 lists all published economic studies that met the inclusion criteria but that were excluded following appraisal of applicability and methodological quality. The following health economic analyses were selectively excluded from the assessment under the justification that a more applicable UK cost utility analysis (Fairbairn 2013) was available: • Armoiry 2018 • Geisler 2017 • Health Quality Ontario 2016 • Santarpino 2017 • Pvero 2018 • Sehatzadeh 2012 • Sehatzadeh 2013 • Spanga 2017 • Wijeysundera 2016 However, Fairbairn 2013 was also excluded due to potentially serious methodological limitations. In particular, the source used to cost the intervention was assessed to be not reflective of the reality of the NHS as the estimated cost of a full TAVI intervention (£16,500) was found to be lower than the cost of the device alone.	device with a range including the current average price of TAVI reported by the NHS Supply Chain. Consequently, we think that the inclusion of Fairbairn 2013 justifies the selective exclusion of the other studies mentioned. It was clear from the evidence review that differences in costs in different settings play a major role in determining the results of a health economics analysis on TAVI: not only the price of a TAVI valve is extremely heterogenous across country, but practice varies as well, as in some countries ICU and LOS after a TAVI or SAVR are not comparable with UK current practice. Therefore, it was agreed that, in the presence of an analysis conducted in the UK, this would be preferred to studies conducted in other settings.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We therefore recommend that NICE reassess the studies listed above and include those which in fact are relevant and should have been included given that Fairbairn 2013 was excluded. Specifically, we would like to point out that while costs in other countries differ, the modelled outcomes can more readily be transferred (that is, the projected QALY gains for SAVR and TAVI, and resulting incremental QALY gain). Especially in light of some of the concerns raised about the modelling of survival, we believe it is important for the committee to understand how QALY projections in the current model compare to those in prior peer-reviewed publications.	
Medtronic Limited	General	0121.5.3	008-009	We note that the hyperlink to the NHS England's Commissioning Policy for TAVI is directed to the 2013 policy. NHS England have a target date to review this policy in Q3 2021/22. Medtronic kindly request that when the NHS England policy is revised the hyperlink is directed to the new document and not the 2013 version which is widely considered to be outdated.	Thank you for your comment. NICE will ensure the link is updated.
Medtronic Limited	Guideline	004	002-013	**Medtronic recommends consideration for broader criteria for referral for echocardiography** Gardezi et al (2018) concluded 'cardiac auscultation has limited accuracy for the detection of VHD in asymptomatic patients and is a poor diagnostic screening tool in primary care, particularly for overweight subjects.' The author further comments that physician auscultation lacks both sensitivity (up to 43%) and specificity (69%) for diagnosing significant valvular heart disease.	Thank you for your comment. The committee agreed that there is limited evidence to indicate that a murmur is a signs of heart valve disease. However, when the nature of the murmur, family history, age or medical history suggest possible valve disease, echocardiography should be considered to establish a diagnosis.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Given the burden of undiagnosed moderate or severe heart valve disease described by d'Arcy JL et al (2016) Medtronic recommends broader criteria for referral for echocardiography to remove the reliance on practitioner auscultation. Consideration for echocardiography could include chronic obstructive pulmonary disease with disproportionate breathlessness, raised B-type natriuretic peptide levels, cardiac symptoms or atrial fibrillation.  **Figure 4** UK population projections of diagnosed and undiagnosed significant valvular heart disease. Diagnosed estimates are based on the number excluded from participation in the present study due to a prior diagnosis of valvular heart disease. Undiagnosed estimates are based on the number with newly diagnosed significant valvular heart disease in OxVALVE-PCS.	COPD with disproportionate breathlessness was not included in the evidence review protocol. The parameters for indications for echocardiography included in the evidence review can be found in appendix A in evidence review A. Recommendation 1.1.1 now refers to atrial fibrillation.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				REFERENCES: • *Gardezi SKM, Myerson SG, Chambers J, Coffey S, d'Arcy J, Hobbs FDR, Holt J, Kennedy A, Loudon M, Prendergast A, Prothero A, Wilson J, Prendergast BD. Cardiac auscultation poorly predicts the presence of valvular heart disease in asymptomatic primary care patients. Heart. 2018 Nov;104(22):1832-1835. doi: 10.1136/heartjnl-2018-313082. Epub 2018 May 24. PMID: 29794244.* • *d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, Frangou E, Farmer AJ, Mant D, Wilson J, Myerson SG, Prendergast BD. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J. 2016 Dec 14;37(47):3515-3522. doi: 10.1093/eurheartj/ehw229. Epub 2016 Jun 26. PMID: 27354049; PMCID: PMC5216199* • *Mangione S, Nieman LZ. Cardiac auscultatory skills of internal medicine and family practice trainees. A comparison of diagnostic proficiency. JAMA 1997;278:717-22.* • *Thoenes M, Bramlage P, Zamorano P, et al. Patient screening for early detection of aortic stenosis (AS)-review of current practice and future perspectives. J Thorac Dis2018;10:5584-94.*	
Medtronic Limited	Guideline	005	013 - 015	**Medtronic believes specific guidance should be given for patients presenting with breathlessness** The NHS Long Term Plan (2019) states 'greater access to echocardiography in primary care will improve the investigation of those	Thank you for your comment. The committee agreed that based on the evidence presented, the specificity values for heart valve disease detection when murmur + other

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				with breathlessness, and the early detection of heart failure and valve disease.' Consequently, Medtronic believes specific guidance should be given for patients presenting with breathlessness opposed to a hyperlink to the Chronic Heart Failure guidelines which may cause confusion, especially given that criteria for breathlessness is not directly/clearly referenced in the Heart Failure guidelines: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf https://www.nice.org.uk/guidance/ng106	symptoms or signs (including atrial fibrillation or left ventricular hypertrophy on ECG, or symptoms or signs of heart failure such as breathlessness) was detected were generally higher than those for murmur alone, suggesting a stronger argument for echocardiography referral in this group of people. However, these observations were only based on a few studies. Therefore, a recommendation was made that echocardiography referral should be offered in individuals with a murmur and other symptoms or signs in line with current practice, but based on the limitations of the evidence this was also limited to those in whom heart valve disease was considered to be a possible explanation of these signs and symptoms. The CHF guidance does not include recommendations on signs of CHF but does include recommendations on criteria for a diagnosis.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medtronic Limited	Guideline	007 027	001 - 005 001 - 009	**Considering the weak evidence for statin therapy Medtronic suggests 'to improve prognosis' is misleading and the guideline should align with the ESC/EACTS Guidance (2017) which states 'no medical therapy for aortic stenosis can improve outcome compared with the natural history.'** Whilst retrospective studies and the RAAVE trial (prospective nonrandomized) showed promising effects of statin therapy, none of the four randomised controlled trials (SALTIRE, TASS, ASTRONOMER, PROCAS) supported the hypothesis that statin treatment would reduce the progression of aortic stenosis. Considering the weak evidence for statin therapy Medtronic suggest the title on line 2 'to improve prognosis' is misleading and could result in the unintended consequence of GPs prescribing medication when it is clear that all symptomatic severe patients (and other patient groups as outlined later in the guideline) should be offered an intervention. We recommend that NICE should align with the ESC/EACTS Guidance (2017) which states 'no medical therapy for aortic stenosis can improve outcome compared with the natural history. Randomized trials have consistently shown that statins do not affect the progression of aortic stenosis.' Please note that the updated ESC/EACTS Guidance on Heart Valve Disease is due for imminent publication. **REFERENCES:** • Moura LM, Ramos SF, Zamorano JL, Barros IM, Azevedo LF, Rocha-Gonçalves F, Rajamannan NM. Rosuvastatin affecting aortic	Thank you for your comment. We have removed the recommendation on statins.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				valve endothelium to slow the progression of aortic stenosis. J Am Coll Cardiol. 2007 Feb 6;49(5):554-61. doi: 10.1016/j.jacc.2006.07.072. Epub 2007 Jan 22. PMID: 17276178; PMCID: PMC3951859. • Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA, Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med (2005) 352:2389–2397. • Chan KL, Teo K, Tam J, Dumesnil JG. Rationale, design, and baseline characteristics of a randomized trial to assess the effect of cholesterol lowering on the progression of aortic stenosis: the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial. Am Heart J (2007) 153:925–931. • van der Linde D, Yap SC, van Dijk AP, Budts W, Pieper PG, van der Burgh PH, Mulder BJ, Witsenburg M, Cuypers JA, Lindemans J, Takkenberg JJ, Roos-Hesselink JW. Effects of rosuvastatin on progression of stenosis in adult patients with congenital aortic stenosis (PROCAS Trial).Am J Cardiol. 2011; 108:265–271. doi: 10.1016/j.amjcard.2011.03.032 • Dichtl W, Alber HF, Feuchtner GM, Hintringer F, Reinthaler M, Bartel T, Süssenbacher A, Grander W, Ulmer H, Pachinger O, Müller S. Prognosis and risk factors in patients with asymptomatic aortic stenosis and their modulation by atorvastatin (20 mg).Am J Cardiol. 2008; 102:743–748. doi: 10.1016/j.amjcard.2008.04.060.	

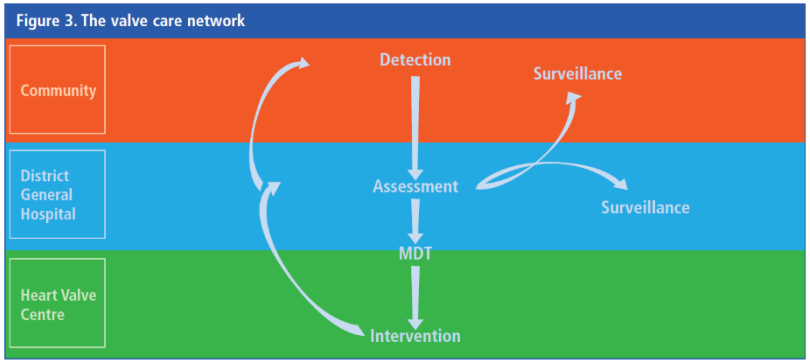
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Valvular-Heart-Disease-Management-of	
Medtronic Limited	Guideline	008	005 - 023	Section 1.3.1 states 'Offer an intervention to adults with symptomatic severe heart valve disease' however Medtronic believe it is unclear progressing straight to guidance on asymptomatic patients with Aortic Stenosis in section 1.3.2 without first addressing symptomatic severe aortic stenosis. It is not standard practice for echo reports to dictate referral or treatment decisions. Therefore, to provide more clarity to practitioners in receipt of a patient's echo report, we recommend the addition of a section specifically for symptomatic severe aortic stenosis which outlines the echo criteria as in sections 1.3.2 and 1.3.3. '**Offer an intervention to adults with symptomatic severe aortic stenosis as defined by the following:** • **Peak velocity (m/s) >4.0** • **Mean pressure drop (mmHg) >40** • **Valve area (cm^2) <1.0** • **Velocity ratio (m/s) ≤0.25 (British Heart Foundation, 2011)'** **REFERENCE:** • https://www.bhf.org.uk/informationsupport/publications/tests-for-heart-conditions/echocardiography-guidelines-for-valve-quantification	Thank you for your comment. 1.3.1 refers to all types of symptomatic severe valve disease, including aortic stenosis. A hyperlink to these echo criteria is included in the 'Terms used in this guideline' section. This is linked to in recommendation 1.1.7.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medtronic Limited	Guideline	008	006 & 007	In section 1.3.2 the draft guidance states 'Consider referring adults with asymptomatic severe aortic stenosis for surgery, if suitable, if they have any of the following.' Given that this section is about "Indications for Interventions", and it is possible that an asymptomatic severe patient could be unsuitable for surgery, we recommend the statement is changed to the following: 'Consider referring adults with asymptomatic severe aortic stenosis **for intervention**, if suitable, if they have any of the following.'	Thank you for your comment. We have made the edit you suggest. However, we revised the economic model based on stakeholder comments. We have changed the recommendations and TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Medtronic Limited	Guideline	008	006 & 007	**To align with current clinical practice, Medtronic suggest that suitability for intervention should be determined by a multidisciplinary heart team combined with informed patient choice as outlined in section 1.5**. Chambers et al (2017) stress 'a multidisciplinary approach is recommended for all types of valve disease.' The British Heart Valve Society publication *Network Based Care for Heart Valve Disease* (2020) stipulates 'assessment of patients with HVD considered for treatment should be undertaken by a multidisciplinary heart	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite

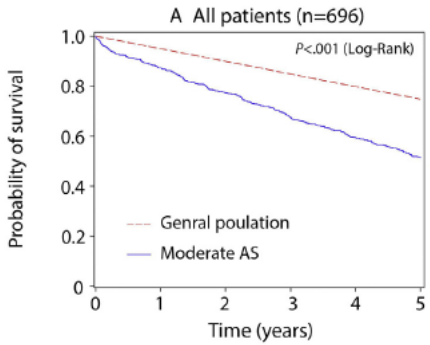
Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				valve team (MDT) in a heart valve centre.'  **REFERENCES:** • Chambers J, Prendergast B, Lung B, Rosenhek R, Zamorano JL, Pierard LA, Modine T, Falk V, Kappetein P, Pibarot P, Sundt T, Baumgartner H, Bax J, Lancellotti P; Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. Eur Heart J 2017; 38 (28): 2177–2182. doi: 10.1093/eurheartj/ehx370 https://www.bhvs.org.uk/bhvs-blueprint/	MDTs as an example of how this may be provided.
Medtronic Limited	Guideline	009	001 - 003	**1.3.5 "distribution of calcium" seems misplaced in this section and should be moved to "Decisions about Interventions" section along with other patient anatomy considerations e.g. risk of Patient Prosthesis Mismatch.**	Thank you for your comment. This is in the appropriate section because the recommendation was derived from the evidence in the review on indications for intervention. This is referenced in

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We agree that distribution of calcium is one of many important considerations (anatomical or otherwise) that should be taken into account when deciding which treatment option is suitable for the individual patient. However, it is clear that this "Aortic Stenosis" section on page 9 is more about the need for intervention rather than decisions regarding the type of intervention. We therefore suggest that statement 1.3.5 is moved to page 12 underneath statement 1.5.4. For information on other anatomical characteristics that should be considered to determine the suitability of intervention, please refer to: • Baumgartner, H. *et al.* (2017) '2017 ESC/EACTS Guidelines for the management of valvular heart disease', *European Heart Journal*. Oxford University Press, 38(36), pp. 2739–2786. doi: 10.1093/eurheartj/ehx391. • Otto, C. M. *et al.* (2021) '2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines', *Circulation*. NLM (Medline), 143(5), pp. e72–e227. doi: 10.1161/CIR.0000000000000923. • NICE IPG 586 Transcatheter aortic valve implantation for aortic stenosis, Published date: 26 July 2017. Please note that the updated ESC/EACTS Guidance on Heart Valve Disease is due for imminent publication.	the hyperlink about suitability for TAVI in rec 1.5.4. Other anatomical characteristics were not included in the review protocol criteria for this question (see appendix A evidence review F). Thank you for the references but as they reference other guidelines we are unable to include them in the evidence review. The NICE IPG on TAVI is cross referenced in this guideline 1.5.5.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medtronic Limited	Guideline	010	015	**Medtronic advocate a broader cohort of patients require monitoring if an intervention is 'not currently needed.'** Medtronic suggests that at a minimum patients with moderate aortic stenosis should also be considered for monitoring. Ito et al., (2020) show that that the prognosis of people with moderate AS is much worse compared with the general population, with a survival rate of only 56% at 5 years. Furthermore patients with decreased LVEFs and/or SVIs were at high risk for all-cause mortality and this deterioration begins before the stenosis becomes severe. Further references to highlight this are listed below.  **REFERENCES:** • Du Y et al., Natural history observations in moderate aortic stenosis, BMC Cardiovasc Disord, 2021	Thank you for your comment. No evidence was identified for any mild or moderate valve disease. Consensus recommendations could not be made for moderate valve disease as there was considered to be more variation in practice for these populations and the recommendation for asymptomatic severe heart valve disease could not be extrapolated to cover these populations as the difference in severity means they are different in terms of the extent of follow-up required. A consensus recommendation is now made for mild aortic or mitral stenosis (1.4.2). It was therefore agreed that research recommendations would be made to cover these areas, which included asymptomatic mild or moderate valve disease (Appendix J evidence review G). The references have been checked and none of them meet the review protocol criteria (see appendix A evidence review G). The intervention was a specified assessment strategy used for

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Ito S et al., Prognostic Risk Stratification of Patients with Moderate Aortic Stenosis, JASE 2020 • Ito S et al., Prognostic Value of N-Terminal Pro-form B-Type Natriuretic Peptide in Patients with Moderate Aortic stenosis, Am J Cardiol, 2020 • Zhu D et al., Left Ventricular Global Longitudinal strain is associated with long-term outcomes in Moderate Aortic Stenosis, Circulation: CV Imaging, 2020 • Murphy K et al., Clinical and Echocardiographic Predictors of Outcomes in Patients with Moderate (Mean Transvalvular Gradient 20 to 40 mm Hg) Aortic Stenosis, Am J Cardiol, 2019 • Delesalle G et al., Characteristics and Prognosis of Patients with Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction, J Am Heart Assoc, 2019 • Van Gils et al., Prognostic Implications of Moderate Aortic Stenosis in Patinets with Left Ventricular Systolic Dysfunction, J Am Coll Cardiol, 2017	monitoring purposes, followed by appropriate valve intervention, in the specified population.
Medtronic Limited	Guideline	011	016 - 019	Section 1.5.2 states "When surgery is agreed, base the decision on the type of surgery (median sternotomy or minimally invasive surgery) on patient characteristics and patient preferences. If minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre" We believe this statement to be confusing and the overall structure of the recommendation is not consistent with the other types of interventions described in the draft guidance document. We suggest that this statement	Thank you for your comment. The committee agreed that it was important to highlight how to decide on the type of surgery and particularly wanted to emphasise patient preference.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				is simplified to read **"If minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre"**	
Medtronic Limited	Guideline	011	010 - 011	On line 10 the guidance states 'the type of access for surgery (median sternotomy or minimally invasive surgery.)' Given the remit of this section is to ensure that during the consent process patients are told about all treatment options and their advantages and disadvantages, Medtronic believe it should state 'the type of access for intervention (median sternotomy, minimally invasive **or transcatheter.)**'	Thank you for your comment. The recommendations refer to the clinically and cost-effective options for the type of surgery. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). We now therefore refer to transcatheter in the bullet point in recommendation 1.5.1 on type of access.
Medtronic Limited	Guideline	011	009	**Medtronic believe a multidisciplinary approach should be encompassed within 'decisions about interventions.'** Holmes et al (2013) stress the critical role of a multidisciplinary team in 'enhancing the process of patient education and informed consent'	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Chambers et al (2017) elaborate that 'the wishes of the patient will inform the discussion of treatment options at multidisciplinary meetings. The consensus of the meeting will be communicated to the patient and if desired will inform further discussion about the timing and nature of surgery. It may on occasion be appropriate to invite a patient to a discussion about his or her case.' **REFERENCES:** • Holmes D, Rich J, Zoghbi W, Mack M, The Heart Team of Cardiovascular Care, Journal of the American College of Cardiology, Volume 61, Issue 9, 2013, Pages 903-907, ISSN 0735-1097 • Chambers J, Prendergast B, Lung B, Rosenhek R, Zamorano JL, Pierard L, Modine T, Falk V, Kappetein P, Pibarot P, Sundt T, Baumgartner H, Bax J, Lancellotti P; Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. Eur Heart J 2017; 38 (28): 2177–2182. doi: 10.1093/eurheartj/ehx370	assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Medtronic Limited	Guideline	011	009	We would like to highlight that given section 1.5 considers all available interventions, we ask that that the statement provided in section 1.5.1 "the risk associated with the procedure" is changed to "the risk associated with the procedure**s**" given that there is more than one procedure to choose from with multiple access approaches.	Thank you for your comment. We have made the edit as suggested
Medtronic Limited	Guideline	012	003 - 007	**We suggest that the phrase "first-line intervention" is removed from section 1.5.3 as this may lead to confusion. Indeed, the factors outlined in 1.5.1 and the multi-disciplinary heart team approach will lead to different choices of first-line intervention for different patient**	We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				groups. For some patients SAVR would be considered the first-line intervention, for others TAVI would be. Medtronic recognises that not all patients are suitable for surgery, similarly not all patients are suitable for TAVI. It is widely recognised that all patients who are at extreme risk/ inoperable for SAVR, for example, should be offered TAVI as first-line intervention and the data below indicates that this patient group represents a large proportion of patients with severe symptomatic severe aortic stenosis (sSAS). Additionally the majority of multidisciplinary heart teams in the NHS would likely consider the following patients as suitable for TAVI as first-line intervention: patients over 80 years old, older people living with frailty, patients who have had previous cardiac surgery, patients with severe liver or kidney disease. Durko et al. 2018 used meta-analysis to develop an algorithm to estimate the epidemiology of sSAS patients in different risk groups (Durko et al, 2018). Using this algorithm, we can use NHS England population data to estimate the total number of patients who would fall into each risk group per year (ONS, 2019). As shown in the table below, whilst it is true that the low risk (LR) group is the biggest patient cohort as stated in the report, there are many extreme risk (ER) and high risk (HR) patients in NHS England who would be deemed inoperable for SAVR and therefore should not be offered SAVR as "first-line intervention".	at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). See evidence review H for details of the health economic model. NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th>NHS England Population</th><th>Population over 65 (%)</th><th>Population over 65 (#)</th><th>AS Prevalence (0.8%)</th><th>Incidence Severe AS (Prevalence/ 1.8 years)</th><th>AS Symptoms Present Per Year</th><th>Extreme Risk (TAVI and MM):</th><th>% Extreme Risk Suitable for TAVI</th><th>Total ER Patients Suitable for TAVI</th></tr>
<tr><td>55,977,178</td><td>18.2%</td><td>10179253</td><td>81434</td><td>45241</td><td>30900</td><td>12854</td><td>61.7%</td><td>793</td></tr>
</table>

REFERENCES:

Durko et al, Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections Eur Heart J. 2018 Jul 21;39(28):2635-2642. doi: 10.1093/eurheartj/ehy107
https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/clinicalcommissioninggroupmidyearpopulationestimates

</td><td></td></tr>
<tr><td>Medtronic Limited</td><td>Guideline</td><td>012</td><td>003 - 007</td><td>Medtronic suggest suitability for surgery or TAVI should be determined by a multidisciplinary heart team considering individual patient characteristics.

The Cardiology Get It Right First Time (GIRFT) Programme National Specialty Report (2021) states 'MDTs and MDMs are an essential part of cardiology treatment pathways and a core function of the heart team. Guidance is currently being updated by a joint Working Group of the BCS, BCIS, the Society for Cardiothoracic Surgery (SCTS), and the Association for Cardiac Anaesthesia and Critical Care (ACTACC).'

Specifically for valve disease The Cardiology GIRFT Programme National Specialty Report (2021) recommends 'all valve patients should come through a single disease specific portal (aortic or mitral/tricuspid) with a</td><td>Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.</td></tr>
</table>

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				rapid triage protocol to direct obvious cases to surgery/TAVI etc. and with a focus on the more complex cases/less obvious decisions at the MDM.' The Cardiothoracic Surgery GIRFT *Programme National Specialty Report* (2018) concurs stating 'successful outcomes depend on the skills and expertise of highly specialised multidisciplinary teams.' ESC/EACTS (2017) Guidance states 'decision making for intervention should be made by a 'Heart Team' with particular expertise in VHD, comprising cardiologists, cardiac surgeons, imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians and heart failure, electrophysiology or intensive care specialists. The 'Heart Team' approach is particularly advisable in the management of high-risk patients and is also important for other subsets, such as asymptomatic patients where the evaluation of valve reparability is a key component in decision making.' Please note that the updated ESC/EACTS Guidance on Heart valve Disease is due for imminent publication. NICE recognises this concept in the transcatheter aortic valve implantation for aortic stenosis interventional procedures guidance (2017) stating 'patient selection should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging and, when appropriate, a cardiac anaesthetist and a specialist in elderly medicine. The multidisciplinary team should determine the risk level for each patient and the TAVI device most suitable for them.'	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Chambers et al (2017) discuss how 'there should be regular Heart Team meetings to discuss the indications for and timing of intervention.' Further stating 'assessment by relevant non-cardiac specialists (elderly care physician, pulmonologist etc.) should be available for patients with significant comorbidities' Kappetein et al (2012) confer that the 'multi-disciplinary team should convene as a group on a regular basis to review and interpret clinical data to arrive at a consensus on the optimal treatment strategy for each patient.' Furthermore Fletcher et all (2012) demonstrate wider benefits; 'an integrated team effort is essential to the best care for each patient regarding individual management and will assure that evidence-based guidelines, in both treatment and secondary prevention, are implemented.' Medtronic advocates for the committee to consider the statement in the NICE Guidelines for chronic heart failure in adults: diagnosis and management (2018) that 'interdisciplinary working has contributed to better outcomes in heart failure but there is further room to improve the provision of multidisciplinary teams (MDTs) and integrate them more fully into healthcare processes.' **REFERENCES:** • https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2021/02/Cardiology-10-03i-EMBARGOED.pdf • https://www.gettingitrightfirsttime.co.uk/cardiothoracic-surgery-report/	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Valvular-Heart-Disease-Management-of • https://www.nice.org.uk/guidance/ipg586 • Chambers J, Prendergast B, Lung B, Rosenhek R, Zamorano JL, Pierard L, Modine T, Falk V, Kappetein P, Pibarot P, Sundt T, Baumgartner H, Bax J, Lancellotti P; Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. Eur Heart J 2017; 38 (28): 2177–2182. doi: 10.1093/eurheartj/ehx370 • Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012 Oct;33(19):2403-18. doi: 10.1093/eurheartj/ehs255. PMID: 23026477. • Fletcher GF, Berra K, Fletcher BJ, Gilstrap L, Wood MJ. The integrated team approach to the care of the patient with cardiovascular disease. Curr Probl Cardiol. 2012 Sep;37(9):369-97. doi: 10.1016/j.cpcardiol.2012.04.001. PMID: 22884247. • https://www.nice.org.uk/guidance/ng106 Please note that the updated ESC/EACTS Guidance on Heart valve Disease is due for imminent publication.	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medtronic Limited	Guideline	012	003 - 007	**Medtronic question the absence of Comprehensive Geriatric Assessments within the guideline to assess suitability for valve replacement relative to frailty** Comprehensive Geriatric Assessment (CGA) are the gold standard for the management of frailty. The British Geriatric Society *Fit For Frailty* states a 'holistic, multidimensional, interdisciplinary assessment of an individual by a number of specialists of many disciplines in older people's health and has been demonstrated to be associated with improved outcomes in a variety of settings.' **REFERENCES:** • https://www.bgs.org.uk/sites/default/files/content/resources/files/2018-05-23/fff_full.pdf	Thank you for your comment. We now refer to frailty in the definition of suitability for TAVI in the section 'terms used in this guideline'. How this is assessed was not part of the scope of this guideline and would be decided locally.
Medtronic Limited	Guideline	012	003 - 007	**Medtronic support that NICE have been somewhat open in their definition of suitability for SAVR and TAVI.** We feel this, when read alongside the "Decisions about interventions" section (once minor changes are made as outlined elsewhere in our response), appropriately captures the multifactorial and intricate nature of treatment decisions for aortic stenosis patients in the NHS.	Thank you for your comment.
Medtronic Limited	Guideline	012 037 038	006 - 007 011 - 013	**Medtronic feel strongly that the statement 'non-bicuspid' is misleading and reads that bicuspid patients who are unsuitable for surgery should not be offered TAVI.** We believe this contradicts current clinical practice where bicuspid patients who are unsuitable for surgery would be considered by an MDT for	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
			003 - 007	suitability for TAVI. We feel strongly bicuspid patients should have access to treatment and that the implied palliative care should surgery be unsuitable is unethical given the existence of TAVI devices with an indication for bicuspid patients. Furthermore, the statements on page 37 and 38 are contradictory points regarding extrapolating data for SAVR in bicuspid patients but not for TAVR in bicuspid patients. Forrest (2020) comparing TAVI in bicuspid versus tricuspid aortic valves from the TVT Registry (932 bicuspid patient cohort) demonstrated all-cause mortality, stroke, and valve haemodynamics did not differ at 30 days or 1 year between patient groups. The paper reported acceptable safety outcomes with low complication rates. Elbadawi (2019) looked at outcomes of transcatheter versus surgical aortic valve replacement for bicuspid aortic stenosis (975 propensity matched bicuspid in TAVI V SAVR) and concluded similar in hospital mortality versus SAVR. and no difference in cardiogenic shock, AKI, tamponade and stroke. TAVI was associated with lower rates of acute myocardial infarction, post-operative bleeding, vascular complications, and discharge to nursing facility as well as a shorter length of hospital stay. We also recommend NICE consider the following published data that demonstrate the safety and effectiveness of TAVI in bicuspid patients: • Mylotte et al., 2014 • Perlman et al.' 2016	more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Halim et al., 2020 • Tchétché 2020 (Conference Presentation) In the final scope document section 3.1 it was stated that "specific consideration will be given to people with bicuspid aortic valve disease" **Medtronic recommends either removal of 'non-bicuspid' or, to honour section 3.1 of the scope, the inclusion of an additional point that states 'For adults with bicuspid severe aortic stenosis offer surgery and if unsuitable refer to an MDT to consider TAVI'.** **REFERENCES:** • Forrest JK, Kaple RK, Ramlawi B, Gleason TG, Meduri CU, Yakubov SJ, Jilaihawi H, Liu F, Reardon MJ. Transcatheter Aortic Valve Replacement in Bicuspid Versus Tricuspid Aortic Valves From the STS/ACC TVT Registry. JACC Cardiovasc Interv. 2020 Aug 10;13(15):1749-1759. doi: 10.1016/j.jcin.2020.03.022. Epub 2020 May 27. PMID: 32473890. • Elbadawi A, Saad M, Elgendy IY, Barssoum K, Omer MA, Soliman A, Almahmoud MF, Ogunbayo GO, Mentias A, Gilani S, Jneid H, Aronow HD, Kleiman N, Abbott JD. Temporal Trends and Outcomes of Transcatheter Versus Surgical Aortic Valve Replacement for Bicuspid Aortic Valve Stenosis. JACC Cardiovasc Interv. 2019 Sep 23;12(18):1811-1822. doi: 10.1016/j.jcin.2019.06.037. PMID: 31537280. • Mylotte D, Lefevre T, et al, Transcatheter Aortic Valve Replacement in Bicuspid Aortic Valve Disease, Journal of the American College	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				of Cardiology, Volume 64, Issue 22, 2014, Pages 2330-2339, ISSN 0735-1097. • Perlman. G, Blanke. P, et al. Bicuspid Aortic Valve Stenosis: Favorable Early Outcomes With a Next-Generation Transcatheter Heart Valve in a Multicenter Study, JACC: Cardiovascular Interventions, Volume 9, Issue 8, 2016, Pages 817-824, ISSN 1936-8798. • Halim. S, Edwards. F, et al. Outcomes of Transcatheter Aortic Valve Replacement in Patients With Bicuspid Aortic Valve Disease; A Report From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry, 2020, pages 1071–1079. • Tchétché 2020, https://www.pcronline.com/Cases-resources-images/Resources/Course-videos-slides/2020/TAVI-for-bicuspid-valves-with-Evolut	
Medtronic Limited	Guideline	0141.6.1	008-011	Medtronic fully supports the recommendation of either TAVI or SAVR procedures for reintervention and welcome that shared decision making is specifically noted.	Thank you for your comment.
NHS England /NHS Improvement	Guideline	005	001	Referral for urgent specialist assessment or urgent echocardiology - there are only 2 waiting time standards: 2 week wait and routine which is 18 weeks. (PC)	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks.
NHS England /NHS	Guideline	005	001	Referral for urgent specialist assessment or urgent echocardiology - there are only 2 waiting time standards: 2 week wait and routine which is 18 weeks. (PC)	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Improvement					
NHS England /NHS Improvement	Guideline	005	004	NHS England and NHS Improvement endorses the recommendation to offer specialist assessment. The NHS is developing heart valve clinics. This specialist assessment could take place in a heart valve clinic supported by multidisciplinary decision making. NICE could consider amending 1.1.3 by inserting the phrase 'specialist assessment, ideally in a dedicated heart valve clinic' in place of 'specialist assessment'. This could also be considered in recommendation 1.1.9. (CPU)	Thank you for your comment. Service delivery including heart valve clinics were not included in the scope of this guideline. However, we now refer to heart valve clinics as an example of how specialist advice or assessment may be provided in the section 'terms used in this guideline'.
NHS England /NHS Improvement	Guideline	005	004	In line with NHS England and NHS Improvement Cardiac Pathway Improvement Programme guidance, patients with severe symptoms should be seen within 2 weeks, rather than 4. Syncope is, elsewhere in NICE guidance, an indication for review within 2 weeks. Exertional syncope in a patient with a murmur we would argue is equally urgent. NHS England and NHS Improvement suggests changing 1.1.3 from four weeks to two weeks accordingly. (CPU)	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks
NHS England /NHS Improvement	Guideline	005	020	The echocardiogram report would be helpful if it gave explicit instructions to the referring GP about onward referral and this is more likely to therefore improve the referral rate. An even better option would be that the echocardiogram report generates an automatic cardiology referral where appropriate (i.e. moderate to severe valve disease). Why put in the extra step of sending it back to the GP for them to refer? (PC)	Thank you for your comment. We now highlight your point in the committee's discussion of the evidence in evidence review D
NHS England	Guideline	005	020	The echocardiogram report would be helpful if it gave explicit instructions to the referring GP about onward referral and this is more likely to therefore	Thank you for your comment. We now highlight your point in the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
/NHS Improvement				improve the referral rate. An even better option would be that the echocardiogram report generates an automatic cardiology referral where appropriate (i.e. moderate to severe valve disease). Why put in the extra step of sending it back to the GP for them to refer? (PC)	committee's discussion of the evidence in evidence review D
NHS England /NHS Improvement	Guideline	011	013	NHS England and NHS Improvement recognises the importance of shared decision-making and is supportive of this recommendation. NHS England and NHS Improvement would encourage NICE to consider whether there has been sufficient emphasis on shared decision-making throughout the wider document. Other recommendations later in the document may be interpreted as not taking shared decision-making fully into consideration. When considering valve interventions, patients should understand the benefits and risks of all available treatments, including no treatment, to enable shared decision-making. This could include percutaneous options as well as surgical ones. Some stakeholder organisations might see recommendation 1.5.3 as an example of where shared decision making could be further emphasised. (CPU)	Thank you for your comment. The committee agreed that patient choice and shared decision making should be an important part of this guideline and the recommendations promote patient choice for clinical and cost effective interventions (for example recommendations 1.4.1 and 1.5.1). We have added a cross reference to the NICE guideline on shared decision making to recommendation 1.5.1. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
NHS England /NHS Improvement	Guideline	016	9.1.9.2	Would Primary Care and Practice Nurses be able to provide support if given additional training? (CNO)	Thank you for your comment. Depending on the psychological support required it may be possible for primary care and practice nurses to provide this.
NHS England /NHS Improvement	Guideline	016	11.1.9.3	Who will provide the psychological support? (CNO)	Thank you for your comment. Who provides the psychological support will depend on a number of individual factors for example including the type of support required.
NHS England /NHS Improvement	Guideline	017	1.1.9.5	How will Transitional services be incorporated into primary care pathways and will this have a financial impact? (CNO)	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned.
NHS England /NHS Improvement	Guideline	022	022	The committee give a rationale for only referring patients for echocardiology with a non-innocent murmur. Whilst it is accepted that children, young adults and women in pregnancy can develop innocent murmurs, most GPs would be uncomfortable in making that judgement without referring a newly discovered murmur for an echocardiogram. Especially when these new guidelines are published. The line between innocent and not isn't one that most GPs would be comfortable with and unlikely to take that risk. This will also make any medico-legal complaints of alleged neglect problematic for the GP	Thank you for your comment. NICE guidelines are unable to make recommendations on the training of GPs. In the experience and opinion of the committee most GPs and non-cardiology physicians would be able to distinguish between murmurs but they should refer if there is a

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(where an echo was not requested). The only defence would be 'the murmur was clinically innocent when I examined the patient', very difficult to prove either way. Therefore, the assumption that the committee made on this recommendation to avoid the 'increased pressure on echocardiography services and would offer uncertain benefit' would not be fulfilled. There will be a significant increase in referrals as a result of these guidelines. (PC)	suspicion of heart valve disease (recommendation 1.1.1).
NHS England /NHS Improvement	Guideline	022	022	The committee give a rationale for only referring patients for echocardiology with a non-innocent murmur. Whilst it is accepted that children, young adults and women in pregnancy can develop innocent murmurs, most GPs would be uncomfortable in making that judgement without referring a newly discovered murmur for an echocardiogram. Especially when these new guidelines are published. The line between innocent and not isn't one that most GPs would be comfortable with and unlikely to take that risk. This will also make any medico-legal complaints of alleged neglect problematic for the GP (where an echo was not requested). The only defence would be 'the murmur was clinically innocent when I examined the patient', very difficult to prove either way. Therefore, the assumption that the committee made on this recommendation to avoid the 'increased pressure on echocardiography services and would offer uncertain benefit' would not be fulfilled. There will be a significant increase in referrals as a result of these guidelines. (PC)	Thank you for your comment. NICE guidelines are unable to make recommendations on the training of GPs. In the experience and opinion of the committee most GPs and non-cardiology physicians would be able to distinguish between murmurs but they should refer if there is a suspicion of heart valve disease (recommendation 1.1.1).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS England /NHS Improvement	Guideline	023	006	'Systolic murmur with a reduced second heart sound'……. this suggests that frontline GPs have not been involved in creating these guidelines. In a busy GP practice, the generalist GP is unlikely to have developed the skill to discern whether the second sound is slightly reduced. (PC)	Thank you for your comment. A GP was a member of the guideline committee. NICE guidelines are unable to make recommendations on the training of GPs. In the experience and opinion of the committee most GPs and non-cardiology physicians would be able to distinguish between murmurs but they should refer if there is a suspicion of heart valve disease (recommendation 1.1.1). If the individual performing the auscultation does detect reduced second heart sound the patient's journey will be faster, however even if the individual performing the auscultation does not detect reduced second heart sound the patient will be referred for echocardiography because of the murmur or directly for specialist advice depending on symptoms. The committee agreed that this recommendation will at least improve the management of some patients.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS England /NHS Improvement	Guideline	023	006	'Systolic murmur with a reduced second heart sound'……. this suggests that frontline GPs have not been involved in creating these guidelines. In a busy GP practice, the generalist GP is unlikely to have developed the skill to discern whether the second sound is slightly reduced. (PC)	Thank you for your comment. A GP was a member of the guideline committee. NICE guidelines are unable to make recommendations on the training of GPs. In the experience and opinion of the committee most GPs and non-cardiology physicians would be able to distinguish between murmurs but they should refer if there is a suspicion of heart valve disease (recommendation 1.1.1). If the individual performing the auscultation does detect reduced second heart sound the patient's journey will be faster, however even if the individual performing the auscultation does not detect reduced second heart sound the patient will be referred for echocardiography because of the murmur or directly for specialist advice depending on symptoms. The committee agreed that this recommendation will at least improve the management of some patients.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS England /NHS Improvement	Guideline	036	002	NHSEI does recognise that a significant element of the cost base is the cost of the device. NHSEI supports highlighting that manufacturers need to consider how they can offer greater value to the NHS to facilitate wider more cost effective access. (CPU)	Thank you for your comment.
NHS England /NHS Improvement	Guideline	038	017	NHSEI recognises that both current NICE guidance and NHSE current policy supports use of TAVI in patients that would be of high risk for surgery. However, we do not agree that this reflects current practice when both access data and device usage suggests there is variation in access to TAVI due to local decision making. (CPU)	Thank you for your comment. We edited that statement to highlight the fact that, although offering TAVI to high risk should have a minimal impact, offering surgery to intermediate and low risk would likely lead to an important change of practice and improve the efficiency of the NHS.
NHS England /NHS Improvement	Guideline	General	General	Once symptomatic, heart valve disease, particularly severe aortic stenosis, have a significant effect on life expectancy and can heavily influence daily living and quality of life. Post-procedure, the transition to daily living may become a physical, mental and social challenge. The Clinical Policy Unit at NHS England and NHS Improvement strongly suggests that the importance of pre-procedural rehabilitation assessment and referral to post-recovery comprehensive rehabilitation is emphasised. (CPU)	Thank you for your comment. We now highlight the important of rehabilitation in the committee's discussion of the evidence in evidence review H.
NHS England /NHS	Guideline	General	General	NHS England and NHS Improvement would encourage NICE to consider the risks associated with the methodology used to assess the efficacy and cost effectiveness of TAVI compared to cardiac surgery. Members of NHS	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Improvement				England and NHS Improvement's Heart Failure and Heart Valve Disease Expert Advisory Group have noted that the TAVI is an evolving technology. This may mean that real life TAVI complication rates are lower than they were in 2010. Associated hospital costs and long term outcomes are thus likely to have changed. NICE should hence consider updating its QALY estimations relating to TAVI. It would be helpful if NICE included a recommendation for an NIHR trial on TAVI in low risk surgery to offset the issues with the current evidence base. (CPU)	The revised version of the model now takes very seriously into account latest improvements of TAVI technology and it draws data from latest audits and trials. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Research recommendations were prioritised by the committee in areas where evidence was agreed to be most needed. This did not include an RCT of TAVI vs. surgery in the low operative risk population as a number

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of RCTs within this risk group were already identified for this comparison. The recommendation on low risk patients was based on cost effectiveness largely driven by the current valve list price.
NHS England /NHS Improvement	Guideline	General	General	NHS England and NHS Improvement would also recommend the inclusion of PROMs for TAVI and surgical aortic valve replacement as a means of assessing the impact on quality of life in patients, many of whom have multiple co-morbidities. (CPU)	Thank you for your comment. Quality of life was included as an outcome in evidence review H (see appendix A) and the questionnaires do capture aspects of PROMs
NHS England /NHS Improvement	Guideline	General		If the strategy is to ultimately identify more patients with murmurs that have moderate to severe symptoms and treat them more appropriately a better model to consider for commissioners would be a GP with extended role as an intermediate step for GPs who discover a murmur with no symptoms (or an innocent murmur). This GP would have more training and experience in knowing which, if any, needed onward echocardiograms. The average GP would not have the skill set to identify whether a patient with an innocent or asymptomatic murmur could just be reassured. (PC)	Thank you for your comment. NICE guidelines are unable to make recommendations on the training of GPs. In the experience and opinion of the committee most GPs and non-cardiology physicians would be able to distinguish between murmurs but they should refer if there is a suspicion of heart valve disease (recommendation 1.1.1).
NHS England /NHS Improvement	Guideline	General		If the strategy is to ultimately identify more patients with murmurs that have moderate to severe symptoms and treat them more appropriately a better model to consider for commissioners would be a GP with extended role as an intermediate step for GPs who discover a murmur with no symptoms (or an innocent murmur). This GP would have more training and experience in knowing which, if any, needed onward echocardiograms. The average GP	Thank you for your comment. NICE guidelines are unable to make recommendations on the training of GPs. In the experience and opinion of the committee most GPs would be able to distinguish between murmurs

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				would not have the skill set to identify whether a patient with an innocent or asymptomatic murmur could just be reassured. (PC)	but they should refer if there is a suspicion of heart valve disease (recommendation 1.1.1).
Primary Care Cardiovascular Society	Guideline	008	007	It would be useful to have clarification of what is meant by surgery. Does the use of this term include TAVI	Thank you for your comment. The term surgery does not include TAVI. The term intervention is used when referring to surgery or TAVI.
Primary Care Cardiovascular Society	Guideline	010	013	In Section 1.4 there is no clear guidance around surveillance for moderate disease. Patient should be made aware of symptoms for which further advice should be sought. In addition we would recommend that in moderate valve disease a management plan to include details of echocardiography surveillance should be shared with the patient and relevant health care professionals including those in primary care.	Thank you for your comment. No evidence was identified for any mild or moderate valve disease. Consensus recommendations could not be made for mild or moderate valve disease as there was considered to be more variation in practice for these populations and the recommendation for asymptomatic severe heart valve disease could not be extrapolated to cover these populations as the difference in severity means they are different in terms of the extent of follow-up required. It was therefore agreed that research recommendations would be made to cover these areas, which included asymptomatic mild or moderate valve disease. We added your point on

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					management plans to the committee's discussion of the evidence in evidence review D
Primary Care Cardiovascular Society	Guideline	015	009	In Section 1.8 clear guidance around ongoing surveillance (including echocardiography) should be shared with patient and relevant health care professionals following intervention	Thank you for your comment. We agree that the need for ongoing surveillance should be shared with the patient and relevant health care professionals as part of good clinical practice. We have added this to the committee's discussion of the evidence in evidence review K
Primary Care Cardiovascular Society	Guideline	General	General	It would be helpful if guidance around endocarditis prophylaxis was referenced in this document	Thank you for your comment. The NICE guidance on infective endocarditis is referenced in the scope for this guideline https://www.nice.org.uk/guidance/gid-ng10122/documents/final-scope.
Pumping Marvellous Foundation	Guideline	004	004	There are no timeframes to referral to specialist services unlike NG106 Guidelines which timeframe both non-urgent and urgent	Thank you for your comment. In the absence of evidence, the guideline committee were unable to recommend time frames as current practice varies considerably.
Pumping Marvellous	Guideline	004	007	There are no timeframes to referral to specialist services unlike NG106 Guidelines which timeframe both non-urgent and urgent	Thank you for your comment. In the absence of evidence, the guideline committee were unable to recommend

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation					time frames as current practice varies considerably.
Pumping Marvellous Foundation	Guideline	005	004	Why is urgent referral 4 weeks not 2 weeks as per NG106 Guidelines?	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks
Pumping Marvellous Foundation	Guideline	005	007	Why no referral timescale?	Thank you for your comment. A referral timescale of two weeks has been added.
Pumping Marvellous Foundation	Guideline	005	017	How are we informing the patient around symptoms and when should they reinitiate contact with their healthcare professional? This is an ambiguous statement and doesn't help patients make informed decisions around their health. When the patient receives communication about having "mild valve disease" it should be accompanied with patient information about symptoms, deteriorating symptoms and what to do. This could mitigate late presentation and hospital admissions.	Thank you for your comment. The committee have made a new recommendation to monitor people with mild to moderate valve disease every 3-5 yrs (1.4.2). There is also a recommendation 1.9.4 on providing information and advice on disease progression which would include who to contact should this occur.
Pumping	Guideline	008	012	Shouldn't we be stating what the BNP/NTproBNP levels are	Thank you for your comment. As the reference values vary across

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Marvellous Foundation					laboratories the committee did not specify the levels.
Pumping Marvellous Foundation	Guideline	008	013	Be more specific. Which symptoms unmasked?	Thank you for your comment. We believe that in the context of a heart valve disease guideline it should be clear that this refers to symptoms associated with heart valve disease, depending on type. The important point is that the test unmasks the fact that the patient is asymptomatic.
Pumping Marvellous Foundation	Guideline	011	018 - 019	"If minimally invasive surgery is the agreed option and is not available locally, refer the person to another centre." The problem with this statement is that there just isn't the infrastructure to deliver a cohesive service of transcatheter interventions.	Thank you for your comment. The recommendation is on the type of surgery rather than transcatheter interventions. The recommendations ensure that minimally invasive surgery should be offered irrespective of whether it is available locally.
Pumping Marvellous Foundation	Guideline	014	003	Why is medical management in patients, with secondary MR, being preferred to transcatheter edge to edge mitral repair to those patients with heart failure and severe secondary MR if surgery is unsuitable. You are suggesting the prioritisation of treatment for patients with HF and severe MR starting with a "Median Sternotomy" – then medical management? The evidence is excellent for the use of transcatheter edge to edge mitral repair in improving quality of life and mortality in this cohort of patients. I disagree with the committee assertions around the rational for the proposed	Thank you for your comment. Transcatheter edge to edge repair may still be considered but after medical management has been tried first. The health economic model was largely based on results from the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				guidance. When people are diagnosed with heart failure, they are immediately initiated on medications as per the NICE NG106 guidelines and TA679. Valve problems are structural. Secondary MR is structural and if the patient hasn't reacted favourably to medications, then an intervention is required. Many NYHA III patients will probably not be suitable for median sternotomy and therefore the most appropriate intervention would be a transcatheter edge to edge mitral repair, not further medical management. What does medical management mean when the patient is up titrated on evidence-based medication and optimised, secondary MR still exists? I also do not agree with the assertions. I disagree with the commentary from the committee about the trials being small and a lack of reported events. The committee's recommendations fail to help those cohort of patients who have heart failure and severe secondary MR. If I was one of the patients, I would say my only route feels like palliation. As a patient advocate and having followed this conversation for many years I find the outputs wholly unacceptable. Not based on the needs of patients and side lining their opportunity to have a solution to their poor QOL and mortality. These patients are a very sick hf cohort and deserve better. This specific guideline recommendation may lead to decreased quality of life, increased hospital admissions and reduced mortality.	COAPT trial, which covered transcatheter mitral valve repair in severe secondary mitral regurgitation. This trial demonstrated substantial benefits over medical management alone when surgery was unsuitable. However, it was not considered to be cost effective at the current list price. For this reason, edge-to-edge mitral valve repair was not recommended over continued optimal medical management. The discussion about the trials being small with few events reported relates to the trials on surgical repair vs replacement, not transcatheter repair.
Pumping Marvellous Foundation	Guideline	014	003	Another concern with this statement is that gives an option for commissioners, not to treat with transcatheter edge to edge mitral valve repair when this is the most optimal option for the cohort of people with HF and severe secondary MR. "Oh well the guidelines say median sternotomy and if not medical treatment' thus denying people clinically appropriate treatment.	Thank you for your comment. The current recommendation does not preclude mitral edge-to-edge repair being undertaken if medical management fails to control symptoms. We have added a

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					recommendation to make this clearer (1.5.14).
Pumping Marvellous Foundation	Guideline	015	019 - 020	This sentence is very ambiguous and does not help the patient or carer. Where do they get the advice from?	Thank you for your comment. This will vary depending on what services the person or family are in contact with and could include for example a GP or a cardiologist.
Queen Elizabeth Hospital Birmingham	Economic Model Report TAVI	015 021 - 022	General	Between April 2019 and April 2021 our centre has undertaken 361 TAVI procedures. Median age was 82 years. 355 (98.34%) were undertaken with percutaneous, transfemoral access with conscious sedation and no general anaesthesia. 5 cases (1.39%) were undertaken via trans-axillary access and one case (0.28%) was undertaken via trans-caval access. Our centre has undertaken no cases via transapical or transaortic access in the last 5 years. 30 day mortality was observed in 6 cases (1.66%). Stroke was observed in only one patient (0.28%). A new permanent pacemaker was implanted in 25 patients (6.9%). The median length of stay was 2 days. Only one patient (0.3%) required an ITU bed. We believe our data is representative of contemporary UK practice in which transfemoral access is the principal access in over 95% of cases, reflecting the evidence and guidelines supporting transfemoral access as the safest access route for TAVI with the best outcomes.	Thank you for your comment. We revised the model to use baseline risks coming from NICOR audit reflecting UK current practice. Data coming from your centre show slightly lower complication rates but are based on a smaller sample. ICU and hospital LOS are now informed by the UK TAVI trial which gives median figures similar to the those provided by your institution (3 for LOS and 0 for ICU). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Queen Elizabeth Hospital Birmingham	Economic Model Report TAVI	017	Table costs	Since the beginning of our programme in 2008 we have observed only 2 cases of re-intervention following TAVI in 1150 cases (0.2%). In both cases re-intervention was successfully undertaken with redo TAVI. To date we have experienced no cases of re-intervention requiring open heart surgery. The model contained in the economic report indicates a total length of stay in TAVI patients of 6 days in intermediate and 8 days in high-risk patients. For the reasons discussed above these figures are based on outdated THV's and practices and not representative of contemporary THV's and methods of access. As indicated above, in the period April 2019-April 2021, our centre undertook 361 TAVI procedures with a median length of stay of 2 days.	Thank you for your comment. Reintervention treatment effect is now informed by the updated meta-analysis and an alternative rate close to 1 is tested in the sensitivity analysis. In almost all TAVI reinterventions, a TAVI-in-TAVI is performed. The model is now using data from the UK TAVI trial suggesting 0 days of ICU for TAVI patients at low surgical risk in the UK. ICU and hospital length of stay in higher risk groups were calculated using the estimates of hospital resource predictors by Reinhoul

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/) The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Queen Elizabeth Hospital Birmingham	Evidence Review H	133 - 134	005 - 031	There is a conspicuous absence of consultation with patient representatives. This contravenes the NHS's own guidelines and standards and must be remedied. Patient representatives should be included in any clinical guideline. In the Evidence Review the relative outcomes of TAVI and surgery are based on 7 randomised trials. We believe this analysis and conclusions to be fundamentally flawed as many of the trials are now obsolete and not representative of contemporary practice. Many of the trials included transcatheter heart valves which are no longer in use (Sapien, Sapien XT, CoreValve) and access techniques which are no longer practised (transaortic/transapical access). Transaortic/transapical access were found to carry a higher mortality than open heart surgery in the PARTNER 2 study and hence these access routes are now seldom used in the United Kingdom. THV's have also undergone considerable iteration, refinement and improvement with considerably lower profile devices now in routine use that reduce the size of access sheaths and allow a higher portion of patients to be treated via transfemoral access with fewer complications. Many contemporary THVs also now have sealing skirts to reduce paravalvular regurgitation. The vast majority of cases are also now undertaken with conscious sedation and fully percutaneously rather than with general anaesthesia. Techniques of access have also improved with a greater use of micro puncture and ultrasound guidance which have improved the rates of access site complications	Thank you for your comment. There were two lay members on the committee with lived experience of heart valve disease. All committee members had equal status. Although all available trials are still included in the clinical review, the economic model uses only trials on 2nd and 3rd generation valves (SAPIEN 2, SAPIEN 3, and Evolut) to inform relative treatment effects. This was done after a further discussion with the committee as the committee highlighted the importance of capturing efficiency and technological improvements of recent valves. These trials are predominantly on transcatheter approach.
Queen Elizabeth	Evidence	133 - 134	General	A more accurate reflection of contemporary outcomes of transfemoral TAVI versus surgery would be gained by a greater weighting of more contemporary trials (PARTNER 3, Evolut Low Risk, UK TAVI Trial) rather	Thank you for your comment. It was not possible to give higher weighting to the more recent trials in the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Hospital Birmingham	Review H			than inclusion of older trials using, now obsolete THVs, (Sapien, Sapien XT, CoreValve) and routes of access which have now largely been abandoned due to poorer outcomes (transapical/transaortic). A meta-analysis of 4 contemporary trials comparing TAVI with surgery (PARTNER 3, Evolut Low Risk, Notion, SURTAVI (STS<3%)) found statistically lower rates of all cause death and cardiovascular death with TAVI at one year. There were no significant differences between TAVI and surgery for major vascular complications, aortic valve re-intervention and functional class (Kolte et Journal of The American College of Cardiology 2019).	analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. In the revised version of the health economic analysis only recent trials on new generation valves are included, so a weighting was not necessary. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Queen Elizabeth Hospital	Guideline	012	003 - 005	We strongly disagree with the draft guidance statement that suggests that surgery be undertaken if suitable (by median sternotomy or minimally invasive surgery), as first-line intervention for adults with severe aortic stenosis, aortic regurgitation or mixed aortic valve disease.	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Birmingham				The draft guidance contradicts recently published guidelines from the American College of Cardiology/American Heart Association (Nov 2020) which recommend transfemoral TAVI in patients 80 years or greater. In patients 65 to 80 years of age, who are suitable for transfemoral TAVI, either TAVI or surgery may be offered (Class 1) with an emphasis on shared decision making. The draft guidance also contradicts the 2017 European Society of Cardiology/European Association of Cardio Thoracic Surgery Guidelines which give a Class I indication for TAVI in patients who are deemed unsuitable for surgical aortic valve replacement as assessed by the Heart Team. The guidelines also recommend TAVI in elderly, intermediate risk patients (STS or Euroscore II >4%) who are suitable for transfemoral TAVI. The ESC/EACTS guidelines are due for revision in 2021/2022 and will incorporate data from the low risk TAVI trials (PARTNER 3/Evolut Low Risk), it is anticipated that TAVI will be recommended in low-risk patients similar to recommendations from the ACC/AHA 2020 guidelines.	evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. NICE methods ensure that all evidence relevant to the review protocol is included rather than just a selection and reviewed for interpretation. Cost effectiveness is also considered in contrast to most other guidelines. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Queen Elizabeth Hospital Birmingham	Guideline	012	003 - 005	We strongly object to the absence of the Multidisciplinary Heart Team in the draft guideline in the decision making process between TAVI and surgery. The decision between TAVI and surgery is often complex and must take into account clinical factors such as comorbidity and frailty and technical factors such as suitability for transfemoral TAVI/surgery. The importance of the Heart Team in decision-making between TAVI and surgery is emphasised both in international (ACC/AHA, ESC/EACTS) and national (NICE TAVI IPG 2017) guidelines. NICE recommendations must be altered to include the key role of the Heart Team in the decision-making process between TAVI and surgery.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Queen Elizabeth Hospital	Guideline	012	003 - 005	The draft guideline does not place any emphasis on shared decision-making or patient preference. TAVI is less invasive than surgery, is associated with considerably shorter lengths of stay, faster mobilisation and recuperation. It is therefore unsurprising that many patients, and their families, express a preference for TAVI. Patient preference should and	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Birmingham				must be a factor in the decision-making process and must be included in the recommendation.	at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Thank you for your comment. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effectiveness analysis indicated that they were not cost-effective within that population.
Queen Elizabeth Hospital Birmingham	Guideline	012	003 - 005	We believe the draft guidance to lack clarity as to the "suitability" of patients for open heart surgery. Whilst guidance is given as to the suitability of patients for TAVI, little guidance is given as to the suitability of patients for open heart surgery. Although a patient may be deemed "technically suitable" for open heart surgery they may possess clinical characteristics which make them high risk for surgery (frailty, poor lung function, chronic kidney disease, liver failure, cognitive impairment etc). This emphasises the utmost importance of the Heart Team MDT which functions to select the optimal treatment for an individual patient	Thank you for your comment. We have expanded on the definition of suitability for TAVI in section 'terms used in this guideline' which now make it clearer both when TAVI is suitable and when surgery is not. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Queen Elizabeth Hospital	Guideline	012	003 - 005	If the draft guidance were to be implemented a substantial proportion of patients who currently undergo TAVI at our institution would be diverted to surgery. Following the COVID pandemic the waiting times for cardiothoracic surgery at our centre have substantially increased with many now patients now waiting over a year. Diversion of patients with severe	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Birmingham				aortic stenosis from TAVI to surgery would prolong waiting times further. It is well recognised that delays to surgery or TAVI in patients with severe aortic stenosis is associated with increasing mortality (Malaisre et al Ann Thor Surgery 2014). Therefore, diverting patients currently undergoing TAVI to surgery would exacerbate the situation by expanding waiting lists and lengthening the time to surgery which would likely increase mortality by delaying treatment	at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Queen Elizabeth Hospital	Guideline	012	003 - 005	We disagree with the draft guidance which provides no provision for TAVI in patients with bicuspid anatomy who are deemed unsuitable for open heart surgery. Although randomised trials comparing TAVI with surgery did not include patients with bicuspid aortic valve disease there are substantial	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Birmingham				registry data demonstrating that mortality in patients with bicuspid versus tricuspid anatomy, treated by TAVI, have comparable mortality at 30 days and 1 year (Makkar et al JAMA 2019). In light of the very poor survival of medically treated patients with severe aortic stenosis (<10% 5-year survival) we believe recommendation for TAVI should be made in patients with bicuspid anatomy unsuitable for open heart surgery. To not offer TAVI to patients with bicuspid anatomy unsuitable for surgery would also be considered unethical.	covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated in this area.
Queen Elizabeth Hospital Birmingham	Guideline	General	General	The Queen Elizabeth Hospital is a large tertiary Cardiothoracic Centre situated in the West Midlands and serves a population of approximately 1.5 million. A TAVI programme was established in 2008 and to date has treated approximately 1150 patients. The TAVI team at Queen Elizabeth Hospital consists of 2 cardiothoracic surgeons (Mr Moninder Bhabra and Mr Stephen Rooney), 4 interventional cardiologists (Dr Sagar Doshi, Prof Peter Ludman, Prof Jonathan Townend and Dr Adnan Nadir) and TAVI nurse practitioner, Mrs Ewa Lawton	Thank you for your comment.
Roche Diagnostics Limited	Guideline	008	006	Section 1.3.2 recommends referral for surgery in adults with asymptomatic severe aortic stenosis and a BNP/NT-proBNP more than twice the upper limit of normal. However, access to NP testing is highly variable around the country, which creates health inequalities by geographic region. In order for this guidance to be put into practice equitably around the country, we think it is essential that NICE make an explicit recommendation to test BNP/NT-proBNP in adults with asymptomatic severe aortic stenosis. We note that the other indications for referral for surgery are based on echocardiographic symptoms, and an explicit recommendation for echocardiography testing has been made. Additionally, it would help if the committee included a table on what they mean by "twice the upper limit of	Thank you for your comment. In the experience of the committee BNP testing is widely available but point of care testing is not. The committee did not define what is meant by 'twice the upper limit of normal' to allow for variance in the normal values laboratories use. The purpose of this review was to identify indicators for interventions and the recommendation

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				normal" for different ages as we are unsure this criterion will be readily understood by all clinicians making referral decisions on the ground.	does indicate that BNP testing should be considered.
Royal College of Nursing	General			We do not have any comments to add to this guideline. Thank you for giving us the opportunity to contribute.	Thank you for your comment.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	007	016	It is inappropriate to exclude low-risk patients in the Economic model. The most contemporaneous data comparing TAVI and surgery are in low-risk patients. Older low-risk patients already routinely undergo TAVI in the UK (e.g. healthy patients aged 80 or older). The Economic model should be revised to include low-risk patients. The Economic model is based on the same data as the Evidence Review. This is inappropriate for the Economic model for the same reasons outlined above. Specifically:- 1. The data are dominated by older trials which, as described above, are not consistent with current practice, or current outcomes, from TAVI in the UK. As a result, the outcome data and associated costs are not representative of current practice. This will be described in more detail below 2. The data from the UK TAVI trial are not included, and would strengthen the model significantly by representing UK-base data, as well as more contemporary data 3. Readily available UK-specific data on outcomes and costs of TAVI in the UK from the UK TAVI database have not been used, although they are available in the public domain (www.bcis.org.uk)	Thank you for your comment. The committee agreed to include low-risk patients which were added in the economic model and assumed to be, on average, 75 years old. Cost-effectiveness is assessed for this category of people as well. 1. The committee agreed that the model should be based on recent rather than historical data to account for valve efficiency and technological improvement. Therefore, in the base case scenario, treatment effects are calculated using only trials of 2nd and 3rd generation valves: PARTNER 2, PARTNER 3 and Evolut.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				4. Data with trans-apical access should not be included in the Economic model, since trans-apical access is more expensive, has worse outcomes, and is only used in 1.3% of patients in the UK.	2. UK TAVI trial is still unpublished and its effectiveness findings were not included in the meta-analysis. Descriptive statistics data from the trial were used to inform length of hospital stay and ICU days after TAVI and SAVR as those reflect UK practice. 3. TAVI outcomes (baseline risks) were taken from the latest BCIS UK TAVI audit. 4. The trials used to inform the meta-analysis are now predominantly using the transfemoral approach. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	007 009 013	018 2.2.1.2 014 - 022	The Economic model has worked on a Lifetime horizon, and has subsequently based this on a 30-year time-frame, as well as a 'shorter' 13-year time-frame. It is inappropriate to base the model on such a long-term timeframe for the following reasons: 1. There are no RCT data comparing TAVI and surgery beyond 5 years. The economic model was therefore based on estimation of events, rather than real data. 2. The average age of a patient undergoing TAVI in the NHS is 81 years. The average life-expectancy of patients undergoing TAVI is therefore far less than 13 years, let alone 30 years. 3. Comparison of long-term event rates is inappropriate in a comparison of 2 procedures, where events occurring in the peri-procedural phase are largely dependent on the procedure, but events occurring later are largely independent of the procedures. Analysis of long-term events distant from the procedure should be confined to those events which are clearly valve-related i.e. valve haemodynamics, structural valve degeneration, valve failure, re-intervention for valve failure The model should be changed to a short time-frame to preserve accuracy e.g. 5 years.	Thank you for your comment. According to NICE Reference case, time horizon must be long enough to reflect all important differences in costs or outcomes between the technologies being compared. This means that, typically, NICE analyses use time horizon exceeding the duration of the trials. The committee agreed to reduce the time-horizon in the base case scenario to 15 years. This should reflect the average life expectancy of 75 years old TAVI patients, who now populate the low surgical risk category. A period shorter than 15 years was considered inappropriate as some of the consequences of TAVI, such as the higher need for reintervention, would occur later. Nevertheless, several scenario analyses were conducted showing the

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					cost-effectiveness results using different time horizons: 5, 10, 15 and 30 years. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	014	Table	The rate of moderate/severe PVL for TAVI used is 4.63%. This is based on data from old trials with obsolete valve types. With current generation valves the rate of moderate/severe PVL is much less. Only the following trials involved current generation valves: PARTNER 3 Mod/Sev PVL 0.8%; Evolut Low Risk 3.4%. In the UK TAVI registry 2019/20 Mod/Sev PVL rate was 2.3%	Thank you for your comment. We updated our model to use data for PVL that reflects the outcomes of new generation valves (SAPIEN 3). The new rate we use for moderate and severe PVL is 2.7%, which is very close to the percentage reported in the last BCIS audit for TAVI in

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					2019/20 for moderate and severe PVL (3%). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	015 021 - 022	Table	The relative re-intervention rate for TAVI and surgery is highly flawed and has a significant effect on costs. Firstly, It is based on a paper (Ler (2020) that was excluded from the Evidence Review in this same Draft Recommendation. In Evidence Review 8, Appendix I (https://www.nice.org.uk/guidance/gid-ng10122/documents/evidence-review-8) NICE state that they excluded Ler (2020) on the grounds that 'methods are not adequate/unclear'. Secondly, the data included in Ler are from older studies using valves which are now obsolete. These valves were associated with much higher rates of moderate/severe PVL, which was the main reason for re-	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review which did not meet the review protocol criteria (see appendix A in evidence review H), though it was included as an evidence for the model.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intervention after TAVI. Current generation valves have far lower rates of PVL, as has been described above, and hence lower rates of re-intervention. The Economic model uses the Ler paper to suggest that the Odds Ratio for re-intervention for TAVI vs Surgery is 3.52 at 1 year, 3.55 at 2-3 years, and 3.55 at 5 years. In fact, more contemporary trials, using valves that are actually in current use, are completely different. In PARTNER 3 the rates of aortic valve re-intervention at 1 year for TAVI vs surgery were 0.6% and 0.5% respectively, in Evolut Low Risk they were 0.7% and 0.6% respectively, and in UK TAVI they were 1.1% for TAVI and 1.6% for surgery. In other words, no difference in re-intervention at 1 year with current generation valves. The use of an odds ration of 3.55 at 1 year in the Economic model is therefore clearly inappropriate. Finally, the model assumes that the relative rate of re-intervention for TAVI and SAVR will be the same over a 30-year time period. This is clearly flawed since there are no data beyond 5 years. More specifically, re-intervention in the first 5 years for TAVI will be predominantly for paravalvular AR. After 5 years paravalvular AR will no longer be a cause of re-intervention. Re-intervention after 5 years for TAVI and SAVR will be mainly for structural valve degeneration, which will happen with both TAVI and SAVR, with no evidence to suggest a higher rate for TAVI. It is therefore wrong to assume that the relative rate of re-intervention after 5 years will be the same as it was in the first 5 years. Figure 6 illustrates how flawed the model's assumptions on re-intervention are, suggesting as it	After further discussion, the committee agreed to exclude this evidence as it was clearly focused on old generation valves not reflecting contemporary practice, as your comment highlighted. Relative treatment effects for reintervention now come from the trials included in the literature review as these were fully discussed and reviewed by the committee. In the base case we are now only using the treatment effect captured in trials evaluating 2nd and 3rd generation valves: • PARTNER 2 • PARTNER 3 • EVOLUT In a sensitivity analysis we use instead Evolut and PARTNER 3 only, with a relative risk close to 1. We are aware that a major challenge of this model is the extrapolation of treatment effects beyond 5 years as

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				does that the relative rate for TAVI to SAVR will be approximately 3.5:1 annually in perpetuity.	trials usually have a shorter follow-up. As per NICE reference case, we use a longer time-horizon (of 15 years) in order to capture all important differences in costs or outcomes between the technologies being compared. We are aware that there might be more uncertainty around outcomes in the longer term. Therefore, scenario analyses have been conducted for several alternative time horizons (5, 10, 30 years). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	017	Table - costs	The data used on costs of ICU stay for TAVI are inappropriate. The Model has based costs on an average ICU stay of 2 days for intermediate risk patients, and 3 days for high-risk. These assumptions are based on data from the trials which are a. old b. reflect the US model of care for TAVI. Currently in the NHS patients do not go to ICU at all after TAVI. The average number of days on ICU for TAVI in the NHS is Zero for intermediate risk and Zero for high-risk. These data are evident from the UK TAVI trial, in which the median length of stay on ICU was 0 days for TAVI (inter-quartile range 0,0), versus median 1 day (IQR 1,3) for surgery. This has led to a major overestimation of the costs of the TAVI procedure.	Thank you for your comment. After further discussion, the committee agreed to use UK data for length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	017	Table - costs	The data used for Total Length of Stay are also inappropriate. The model uses a LOS of 6 and 8 days for TAVI in intermediate and high risk respectively vs 9 and 11 days for surgery. This is very far from current practice for TAVI. Hospital stay was much lower in PARTNER 3 and Evolut Low Risk. The UK TAVI trial data show median LOS 3 days for TAVI vs 8 days for SAVR. UK TAVI registry data show median LOS 2 days for TAVI. This has further contributed to overestimation of the costs of the TAVI procedure.	Thank you for your comment. After further discussion, the committee agreed to use UK data for length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	042	Table 30	Table 30 shows the events per 1000 patients in the Economic model and demonstrates the use of inappropriate data drawn from old trials that are not reflective of contemporary TAVI practice and outcomes ; In particular:- a. Stroke. The data in the model show that strokes are higher with TAVI. Contemporary studies show lower stroke rate with TAVI (PARTNER 3, Evolut Low Risk), or no difference (UK TAVI). The model did not use data from Evolut Low Risk or UK TAVI despite their greater relevance to contemporary practice. b. Hospitalisation. The data in the model show that hospitalisations far higher with TAVI. Contemporary trials (Evolut Low Risk, PARTNER 3) show far fewer hospitalisations with TAVI. These data are much more contemporary and close to current clinical practice. c. Re-intervention. As described above, the odds ratio used for re-intervention is inappropriate.	Thank you for your comment. a. The meta-analysis used in the base case analysis of the model was updated to include Evolut trial and limited to 2nd and 3rd generation valves only (PARTNER 2, PARTNER 3, Evolut). UK TAVI trial could not be included as it is currently still unpublished. b.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				d. Major bleeding, major vascular complications, pacemaker. All would be lower if the economic model had included Evolut Low Risk and UK TAVI, had given greater weighting to more recent trials and less to older trials, and had excluded non-femoral access	Likewise, the hospitalisation meta-analysis now uses includes trials of second and third generation valves. The studies suggest a higher hospitalisation with SAVR in the first year, but lower for the years beyond the first one. Therefore, the model applies 2 different transition probabilities and hazard ratios. c. Ler 2020 was excluded and reintervention relative treatment effect is now informed by the meta-analysis of the PARTNER 2, PARTNER 3 and the Evolut trial. A scenario analysis with a relative risk close to 1 was tested as well. d. The trials in these revised meta-analyses predominantly used transfemoral access. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Economic Report TAVI	General		I believe that the TAVI Economic Model is significantly flawed. The principal problem with the Economic model is that is constructed using data drawn from old trials of TAVI versus surgery, which are not reflective of current clinical practice, and hence costs, as well as outcomes and their associated costs, are grossly inaccurate, leading to grossly inaccurate assessment of cost-effectiveness. In addition, the costs of the TAVI procedure are significantly overestimated, and are not representative of current NHS TAVI costs. The results of the Economic model are not consistent with previous cost-effectiveness analyses of TAVI.	Thank you for your comment. The model was revised to use only contemporary data reflecting current practice and costs. We think that the current version of the model is reflecting outcomes and costs in the NHS. The length of hospital stay and ICU stay have been revised using UK TAVI trial data. The cost of a TAVI procedure for each risk group (without the valve) was estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					These estimates are in line with the costs provided by several NHS trusts around England. The results of the economic analysis are consistent with previous cost-effectiveness analysis: High risk ICER: • NICE model: £14,000 • Tarride 2019 (Canada): £9,510 (they used a cheaper price for TAVI) Intermediate risk ICER: • NICE model: £50,000 • Kodera 2018 (Japan): £51,210 • Tam 2018 (Canada): £43,055 • Goodall (2019) found that TAVI dominates SAVR but their analysis is using French prices for valves which are priced much lower than the ones in the UK. To give an example, a Sapien 3 valve in France is charged around £12,000 (source:

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI000036577833) whereas the average price of a TAVI valve in the UK is £17,500 (source: NHS Supply Chain). At this price, the NICE model reaches the same conclusion of Goodall • Tarride 2019: £15,500. Though they use a cheaper price for the valve as in Canada Sapien 3 is charged less (£14,500). At the same price, the NICE model assesses TAVI to be cost effective as well. Low risk ICER: • NICE model: £136,000 • Tam 2018: £15,900 but they used Canadian price for Sapien 3 (£14,500). At the same price the NICE model assesses TAVI to be cost effective in low risk patients as well.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Evidence Review H	133	005 - 009	The use of older data including some inappropriate data, and the exclusion of some more contemporary data, means that the relative outcomes of TAVI compared to surgery stated in the Evidence Review are not reflective of contemporary data. Specifically:- a. The Evidence Review states that there is a signal of harm for mortality for TAVI at 12 months. However, all of the 3 most recent trials (PARTNER 3, Evolut Low Risk, UK TAVI) showed lower 12-month mortality with TAVI than surgery. Published meta-analyses have also consistently shown lower 12-month mortality with TAVI. The Evidence review includes some previous meta-analyses, but has excluded published meta-analyses of the trials of TAVI vs SAVR for Low surgical risk patients. These published meta-analyses all	Thank you for your comment. Evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes) and is not restricted to 12 months. Published meta-analyses that were excluded were used to identify studies relevant to this review and all relevant studies in the low-risk

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				show superior 1-year outcomes for TAVI. There is no reason for them to have been excluded Furthernore, the Committee's own meta-analysis in the Economic model shows a very strong trend for reduced 12-month mortality, even though it has excluded data from Evolut Low-risk and UK-TAVI, both of which were associated with numerically reduced 12-month mortality for TAVI vs SAVR. b. The Evidence Review states that there is a signal of harm for TAVI with re-hospitalisation. Both PARTNER 3 and Evolut Low Risk showed substantially and significantly reduced hospitalisation at 12 months for TAVI. The Evidence review has not included the Evolut Low risk data. The Evolut Low risk trial publication includes the incidence of re-hospitalisation for heart failure at 12 months, which is 6.5% for surgery vs 3.2% for TAVI.	population were included in evidence review H. The health economics analysis took a different approach as we were interested to capture short-term mortality benefits to assess cost-effectiveness. Hence, we looked at mortality benefits at 1 and 2 years and assumed no benefit in the long-term, as found in the clinical review. We note also that the risk ratios or hazard ratios did not suggest large differences between the two groups for these outcomes but the committee considered any difference in mortality based on the absolute risk difference to be important. This is described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for

					most outcomes and the role health economic modelling had in the decision process. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. In the model hospitalisation was revised by distinguishing between hospitalisation in the first year and in second year. The evidence suggests that hospitalisation is lower with TAVI in the first year, but higher beyond that. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Royal Papworth Hospital NHS Foundation Trust	Evidence Review H	133	014	The Evidence Review concludes that TAVI is associated with a significantly higher rate of re-intervention than surgery. However, the data this is based on are flawed. Firstly, the data come from 1 trial only (PARTNER 2). Secondly, the TAVI valve used in this trial (SAPIEN XT) is no longer available, having been superseded by a newer iteration (SAPIEN 3 / SAPIEN 3 Ultra), which has far better procedural outcomes, particularly with respect to paravalvular leak (PVL) / aortic regurgitation, but also to structural valve degeneration (SVD). Published data have shown that SAPIEN 3 has better outcomes up to 5 years compared to SAPIEN XT, with valve haemodynamics and SVD equivalent to SAVR (Pibarot 2020). Thirdly, re-intervention after TAVI is driven primarily by PVL. Since PVL is much less with contemporary valves, re-intervention is also much less. Basing the evidence for the relative risk of re-intervention on 1 study of an outdated TAVI valve is therefore completely inappropriate. In the UK TAVI trial, the rate of re-intervention at 12 months was 2.2% for TAVI versus 2.9% for SAVR. These data are UK-based, far more contemporary, and would have been much more appropriately used than the PARTNER 2 data.	Thank you for your comment. Data on the need for re-intervention outcome was available from 6 further trials in addition to PARTNER 2, but these were analysed separately because only PARTNER2 reported this as a time-to-event outcome. All data were considered when the committee discussed the evidence. In the revised version of the model, reintervention risk ratio is calculated using studies on 2nd and 3rd generation valves. A scenario analysis where this figure is calculated from the Evolut and PARTNER 3 only was conducted as well. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. The point about need for re-intervention possibly reducing with more contemporary valves was discussed with the committee and incorporated into the discussion section of the evidence review. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal Papworth Hospital NHS Foundation Trust	Evidence Review H	133 - 134	005 - 031	The Evidence Review summarises the relative outcomes of TAVI and surgery based on the data from the 7 trials included. Once again, the inclusion of inappropriate data has resulted in the presentation of relative outcome data for surgery and TAVI which is not representative of current outcomes from TAVI in the UK. As outlined above, if the committee had excluded STACCATO, excluded Trans-apical and Trans-aortic data, given greater weighting to the more recent and more contemporary trials, and included the UK TAVI trial, the relative outcomes of TAVI and surgery would have been more appropriate, more reflective of current outcomes, and less biased against TAVI, since TAVI procedure and outcomes have changed far more over the past 15 years than those of surgery.	Thank you for your comment. It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. In the revised version of health economic analysis, only recent trials on new generation valves are included, so a weighting was not necessary. However, although the STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol, it had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has now been excluded from the economic modelling based on the transapical access route not being in line with current practice. The UK TAVI trial data are not yet published in a peer-reviewed journal

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow at present, and we have sufficient published data with longer-term follow-up. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal Papworth Hospital NHS Foundation Trust	Guideline	009	013 - 014	In addition to the above comments I believe that there are some flaws in the evidence review comparing TAVI with surgery. These flaws can be summarised as an over-reliance on the inclusion of older data which are not consistent with current clinical practice, and hence the outcomes of which are not consistent with current outcomes from TAVI in the NHS. Specifically:- 1. The STACCATO trial should not be included. This trial included 100% Trans-apical access for TAVI. In the UK in 2019-20, Trans-apical access was used in 1.3% of TAVI cases (UK TAVI Registry Data, www.bcis.org.uk). Outcomes from trans-apical TAVI are worse in all trials, which is precisely why it is not used in current practice. 2. The data on Trans-apical TAVI from the PARTNER 1A & PARTNER 2 trials should not be included. In these trials 29.9% and 23.9% of TAVI procedures respectively were trans-apical. The Evidence review should focus on the data from trans-femoral TAVI, which is the dominant access route in contemporary practice (96.9% of TAVI procedures in the UK in 2019-20). 3. The data on Trans-aortic / Direct aortic TAVI in the Corevalve High-risk (17.1% Trans-aortic) and SURTAVI (4.1% Trans-aortic) trials should be excluded. Like Trans-apical access, Trans-aortic access is associated with worse outcomes, and is no longer used in contemporary practice (<0.5% UK TAVI Registry 2019-20)	Thank you for your comment. The committee has considered these points as follows: 1.The STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has been excluded from the economic modelling based on the transapical access route not being in line with current practice. 2.The committee agrees that the proportion of transapical procedures are higher than in current UK practice. However, the committee does not believe that across the UK the proportion of patients having transapical TAVI is 0% and so in line with the review protocol, the PARTNER trial data have been included as a combined data for transfemoral and transapical TAVI.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				4. The Evidence review should have analysed the trans-femoral TAVI data separately, as has been done within all of the included trials, and within multiple previous meta-analyses. A comparison of trans-femoral TAVI and surgical AVR would be far more relevant to current practice. This was the approach taken in the ESC/EACTS and in the ACC/AHA guidelines. 5. The Review should give greater weighting to more contemporary trials which are more reflective of current practice and outcomes. The PARTNER 1A trial began recruiting in 2007, and the CoreValve High Risk trial in 2010. Both PARTNER 2A and SURTAVI are also older trials which do not reflect current clinical practice. The following are specific examples of how the older trials bear no resemblance to current clinical practice, whereas the more contemporary trials (PARTNER 3 and Evolut Low Risk) are much closer to current practice, evidenced by the latest data from the UK TAVI Registry 2019-20 (www.bcis.org.uk) a. TAVI Valve type. All of the above trials used valve technology that is obsolete. These older valves were associated with far higher rates of valve-related complications, specifically paravalvular aortic regurgitation, but also pacemaker implantation, valve embolization, need for re-intervention etc. b. Access route. Trans-femoral access is associated with superior outcomes. Rate of trans-femoral access in the trials included compared to UK TAVI registry data was as follows: PARTNER 1A 70.1%, Corevalve High Risk 82.8%, PARTNER 2 76.7%, SURTAVI 93.6%, NOTION 96.5%, PARTNER 3 100%, Evolut Low Risk 99.0%, UK TAVI Registry 96.9% c. General anaesthesia. GA means a longer procedure, slower recovery, longer hospital stay, and greater use of resources. Rate of GA in	3.Similarly, the CoreValve high risk and SURTAVI trial data cannot be excluded from the analysis post-hoc. Additionally, it would be inappropriate to exclude the CoreValve study as it is one of only few trials in the high risk cohort. 4.TAVI route of access was included as a subgroup analysis to explore it heterogeneity was found, and not as a stratification factor in the clinical review. There were not large differences in effect estimate between the overall analysis and the transfemoral subgroup analysis. As the recommendation was driven by the cost effectiveness evidence no changes have been made to the clinical review regarding the route of access as this would not affect the conclusions of the committee. In the revised version of the health economic model, only recent trials on 2nd and 3rd generations valves were used to estimate relative

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the trials included in which it was reported compared to UK TAVI registry data was as follows: Corevalve High Risk 94.6%, SURTAVI 75.7%, NOTION 81.7%, PARTNER 3 34.9%, Evolut Low Risk 56.9%, UK TAVI Registry 9.3% 6. The Evidence Review should have included data from the UK TAVI trial, which have been presented at a major international conference (American College of Cardiology 2020), and hence are in the public domain. Although not published in a peer-review journal, (currently under review) these data have huge value in being 100% UK-based, and in being more contemporary than most of the included trials.	treatment effects. Those are prevalently on transfemoral approach. 5. It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. In the revised version of the health economic analysis only recent trials on new generation valves are included, so a weighting was not necessary. a.The committee acknowledge that the older valve types are associated with higher rates of valve complications. However, only 3 studies used 2nd or 3rd generation devices. Only the outcomes of these studies were used in the health economic model to better represent contemporary practice. c.The committee acknowledge that general anaesthesia is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					required much less often for TAVI in current practice than historically. However, as above, it was not considered to be appropriate to exclude older trials from the main analysis in the clinical review. 6.The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow at present, and we have sufficient published data with longer-term follow-up.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	1. The Recommendation is in complete contradiction to international guidelines. The 2017 European Society of Cardiology & European Association of Cardiothoracic Surgery guidelines give TAVI a Class 1 indication for patients unsuitable for surgery, and for patients at high and intermediate surgical risk "with TAVI favoured in elderly patients suitable for trans-	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				femoral access". These Guidelines were produced before the publication of the Low-risk trials, and are due to be updated later in 2021, when they are likely to approve TAVI in low surgical risk patients. The 2020 American College of Cardiology / American Heart Association guidelines give a Class 1 indication for TAVI, specifically recommending that trans-femoral TAVI is preferred to surgery in patients aged over 80, or younger with a life-expectancy of 10 years or less, and that in patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery is recommended based on shared decision-making.	effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation.
Royal Papworth Hospital NHS	Guideline	012	003 - 005	2. The recommendations do not take any account of individual patient considerations, in particular age, life expectancy, frailty, co-morbidity, anatomical suitability for trans-femoral TAVI, and how these factors influence the best treatment options for patients.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation Trust					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					they were not cost-effective within that population.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	3. The recommendation does not include appropriate reference to the role of the multi-disciplinary Heart team (MDT), and shared decision-making. The importance of the MDT is emphasised in all national and international guidance, including the British Heart Valve Society publication 'Network based care for heart valve disease' (2020), GIRFT Cardiothoracic Surgery report (2018), and ESC/EACTS 2017 & ACC/STS 2020 guidelines, as well as the NICE TAVI IPG (2017). Heart team decision-making allows complex individual patient factors such as those outlines in point 2 above to be considered. We believe that the Recommendation should be altered to refer to the importance of the MDT in deciding between TAVI and SAVR.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided. The committee agree that that shared decision making is key and we specifically refer to this in recommendations 1.5.1 and 1.9.1.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	5. The Recommendation would have an enormous and highly detrimental impact on clinical practice. If the proposed guidance were to be followed, there would be a huge fall in the numbers of patients having TAVI, and a huge increase in the numbers of patients having surgery. It would not be possible for surgery to deliver the increased demand, especially in the COVID and post-COVID era, and patients would face huge waits and many would die on the waiting list. Published registry data show that the mortality on a waiting list for surgery is about 4% per month. (Malaisrie, Ann Thorac Surg 2014)	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					interventions are clinically and cost effective. Implementation of these should take the current context into account.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	6. The draft guideline misjudges the impact that would occur if TAVI were to be recommended in patients suitable for surgery. Firstly, as stated above, TAVI is already frequently undertaken in patients suitable for surgery. Secondly, the guideline correctly states that 80% of surgery is in low-risk patients. However, the implication that most or many of these patients would have TAVI if it were recommended is wrong. Surgery is mostly undertaken in very low risk and much younger patients. Average age in the UK is 63 from SCTS published data, whereas average age for TAVI in the UK is 81 (UK TAVI Registry data). In line with international guidelines, TAVI would only be undertaken in low-risk patients over the age of 75-80 and who are suitable for low-risk trans-femoral TAVI for non-bicuspid disease.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention. Recommendations for interventions could not be made for particular populations if the cost-

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effectiveness analysis indicated that they were not cost-effective within that population.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	7. The draft guideline gives no consideration to patient experience and patient preference. TAVI is performed under local anaesthetic, has a median hospital stay of 2-3 days, and immediate recovery. Surgery is highly invasive, involving chest incision, general anaesthetic, intensive care stay, median stay of 8 days in total, and recovery period of 3-6 months, especially in older patients. TAVI is therefore a far preferable experience for patients. Patient preference should always be a factor in clinical decision-making.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	8. The committee did not include any patient representation. Patients should be at the centre of guidelines and decision-making in the NHS. The failure to include patient representation may explain the failure to give sufficient focus to patient preference and patient experience	Thank you for your comment. Two lay members with lived experience were on the committee. The committee acknowledge the importance of shared decision making and have made recommendations to support this 1.5.1 and 1.9.1. We have also added a cross reference to the NICE guideline on shared decision making (1.5.1).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	003 - 005	9. The recommendation would be of particular harm to patients in the context of COVID. TAVI has substantial advantages over SAVR in the COVID and post-COVID era, since there is no requirement for ICU, and hospital stay is far shorter. This is reflected in the much greater fall in the numbers of SAVR cases done in 2020 than the fall seen for TAVI. This fall also means that the backlog of patients requiring treatment for severe AS is substantial. If the proposed guidelines were to be implemented, the massive reduction in TAVI numbers and required increase in SAVR numbers would be impossible to deliver. Even if it were theoretically possible to do this, the increase in ICU usage would have hugely negative implications in hospitals where ICU capacity is under enormous pressure. In contrast, TAVI allows patients to be treated quickly, with short hospital stays, and no use of ICU.	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Royal Papworth Hospital NHS Foundation Trust	Guideline	012	006 - 007	The draft guideline allows no recommendation for TAVI in patients with bicuspid anatomy who are unsuitable for surgery. This is inappropriate. Although randomised trials did not include bicuspid disease, there is a substantial body of evidence from registries evaluating TAVI in bicuspid disease. For example, Forrest (2020) reported outcomes of tricuspid versus bicuspid disease treated by TAVI in the TCT registry, and showed no difference in mortality or stroke at 30 days or 12 months. TAVI in bicuspid anatomy is in routine use in the NHS in inoperable or very high risk surgical patients as medical therapy for severe aortic stenosis which would often be the only option for such patients is associated with extremely poor outcomes.	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.
Royal Papworth	Guideline	012 038	003 – 005	4. The Recommendation is inconsistent with current clinical practice. TAVI is currently in widespread use across the NHS in patients who are suitable for surgery, and who may be categorised as high risk, intermediate	Thank you for your comment. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Hospital NHS Foundation Trust			016	risk, and even low risk, but in whom assessment of the individual patient by the MDT, based on age, life-expectancy, co-morbidities, and anatomy, leads to a recommendation of TAVI. For example, across the NHS TAVI would be considered first-line therapy for the following groups: Patients aged 80 or over, patients with frailty, patients with cognitive impairment, patients who have undergone previous cardiac surgery, patients with liver disease, patients with severe kidney disease etc. This is currently the practice that we follow at Royal Papworth Hospital with excellent results for our patients. In contrast to this reality, the draft consultation states that "The committee agreed that TAVI is usually reserved for when surgery is not suitable. The guidelines therefore reflect current clinical practice". Although the term 'suitable' is not defined in the current guidance I am concerned that the term suitable will be interpreted as 'inoperable' which would be in complete contradiction with current practice. For at least 10 years TAVI has been used widely in patients who would have been considered operable, but high risk. For at least 5 years TAVI has been used in intermediate risk patients, and more recently also for low risk patients, IF the patient is aged at least 75 or older, and IF the patient is anatomically suitable for low-risk non-bicuspid trans-femoral TAVI. This change has been driven by trial evidence, by heart team decision-making, and by patient preference.	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The definition of suitability for TAVI has been expanded (see section 'terms used in this guideline). Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Royal Papworth Hospital NHS Foundation Trust	Guideline	General	General	Royal Papworth Hospital is one of the largest cardiothoracic centres in the country with an expanding and much needed TAVI service. As a lead for the non-coronary intervention and TAVI groups, I find the draft recommendation that all patients with severe aortic stenosis should be offered surgery as first-line treatment, with TAVI considered only for patients who are unsuitable for surgery with non-bicuspid anatomy not in-line with current practice in the UK and completely misaligned to international guidelines. There are a number of reasons that I believe that the draft recommendations on intervention for aortic stenosis by TAVI or surgery is wrong.	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Society for Acute	Guideline	General	General	From our perspective SAM are happy with these recommendations	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medicine					
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	010	014 - 018	Recommendation 1.4.1 SCTS strongly supports the recommendation for regular monitoring in patients who have asymptomatic severe disease. However, we feel that new ways of working post pandemic may offer the opportunity for more regular clinical review of patients. We note that current ESC guidance suggests 6-month intervals for patients with severe asymptomatic valvular heart disease and wonder if there is an opportunity for earlier remote follow up especially for patients with severe disease.	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	011	016 - 019	Recommendation 1.5.2- Interventions SCTS welcomes the recognition by the committee that minimally invasive surgery will play an increasing role in surgery for valve disease. It has become increasingly apparent to SCTS that many patients prefer a minimally invasive approach over a sternotomy if they are suitable. Randomized controlled trials establishing the safety and efficacy of minimally invasive surgery for aortic valve surgery has been published in the UK and a large multicentre National Institute for Health care Research (HTA) funded trial in mitral valve surgery has recently completed recruitment.	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				SCTS recognizes that the provision of minimally invasive valve surgery nationally is not uniform and supports the recommendation that patients are offered the opportunity to move to other surgeons and other units with the expertise to provide this service. SCTS has taken a number of steps to improve the provision and assure the quality of MIS surgery nationally. This includes the establishment of an Innovations sub-committee within SCTS. This recommendation will allow SCTS to establish a formal process to define criteria for surgical and unit expertise to allow safe national dissemination and monitoring of outcomes through a national audit process.	
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	012	002 - 005	Recommendation -1.5.3- Aortic valve disease SCTS strongly supports this recommendation. It is in keeping with outcomes nationally and in line with data published in the National Adult Cardiac Surgery Audit Summary Report of data from 2016/17-2018/19 published in 2020. (https://www.nicor.org.uk/national-cardiac-audit-programme/adult-cardiac-surgery-surgery-audit/). The audit highlights excellent outcomes for patients irrespective of age. In hospital mortality in patients over the age of 80 was 1.2% between 2016-2019 Similarly, the audit confirmed the relationship between risk and in hospital mortality. Contemporary outcomes in the UK are consistently lower than predicted risk scores, and in patients with the highest predicted in-hospital mortality (predicted risk of 8% or higher), mortality was only 5.6% in England.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We support the fact that the document recognizes the clinical and cost effectiveness of surgery for the management of heart valve disease even in the elderly and that it highlights the role of minimal access surgery to improve choices for patients and potentially improve outcomes further. We support the emphasis that the committee has placed on long term clinical and QOL outcomes as well as the emphasis on long term and durable clinical benefit. We stress the role of the multidisciplinary team in the aspects of our response. Input from the MDT about risks not captured in standardised scores e.g. frailty, dementia, and complications other than mortality (e.g. para valvular leaks, pacemaker insertion or patient prosthesis mismatch) will make sure that decision making is patient focused. These complications are often associated with poorer quality of life and or long term survival.	
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	012	006 - 007	Recommendation 1.5.4 SCTS strongly supports this recommendation. The document recognizes the clinical and cost effectiveness of surgery for the management of heart valve disease even in the elderly. However, there are significant numbers of patients with severe symptomatic aortic stenosis who are not suitable for surgical intervention. The emergence of TAVI represents an opportunity to treat those patients. It's important that selection of patients for this technique is made in a multidisciplinary team and that surgeons get the opportunity to assess patients for suitability of surgery prior to transcatheter intervention. Similarly, it is important that patients get the option to meet a cardiac surgeon to discuss options. Frequently patients are anxious about surgery and are influenced by TV, social media, friends and other clinicians and the	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				opportunity to meet a surgeon prior to making a decision is often very useful.	Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline.
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	013	004 - 006	Recommendation 1.5.8 Primary mitral regurgitation SCTS strongly supports this recommendation which is in line with clinical evidence accrued over several decades. However, data from National Adult Cardiac Surgery Audit (NACSA) and for Getting It Right First Time (GIRFT) confirm significant variation in repair rates for PMR nationally. This recommendation allows SCTS to focus on what we perceive as a key quality improvement outcome in cardiac surgery. SCTS is currently working with the British Cardiac Society to develop guidelines for decision making within multidisciplinary heart teams to ensure that patients are referred to surgeons with particular expertise for mitral valve repair.	Thank you for your comment. No evidence was identified on the level of expertise required to carry out the intervention and due to variation in current clinical practice a consensus recommendation could not be made. A research recommendation could not be made because level of expertise was not specified in the review protocol (see evidence review H appendix A).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				SCTS wonders if in this recommendation NICE should be more explicit about the need for patients to be referred to a suitably experienced specialist surgeon or centre.	
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	013	011 - 012	Recommendation 1.5.10 SCTS strongly supports this recommendation. There are significant numbers of patients with severe symptomatic mitral regurgitation who are not suitable for surgical intervention. The emergence of transcatheter edge-to-edge repair therapy represents an opportunity to treat those patients. It's important that selection of patients for this technique is made in a multidisciplinary team and that surgeons get the opportunity to assess patients for suitability of surgery prior to transcatheter edge-to-edge intervention.	Thank you for your comment.
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	General	General	The Society for Cardiothoracic Surgery in Great Britain and Ireland values the opportunity to respond to The National Institute for Health and Care Excellence (NICE) draft guidelines for the investigation and management of heart valve disease in adults. We support all the main recommendations of the draft document and it's our opinion that overall, these recommendations will significantly improve access to care, timely diagnosis, appropriate intervention and outcomes both short and long term, for patients with heart valve disease. As a Society, our main objective is: To advance science in the field of cardiothoracic surgery for the benefit of the public by encouraging and promoting excellence in the practice of cardiothoracic surgery. Over 82% of UK consultant surgeons are members. Our Society has collected data on all valve procedures performed in the UK since 1978. In 2000 this changed from a voluntary registry to a mandated	Thank you for your comment. 1. The protocol for this review was developed as a committee, with the discussion involving input from professionals with different areas of expertise, including those experienced in surgery and TAVI. Where possible, our review reported outcomes individually rather than composite outcomes that studies had reported as their primary outcome. 2.The time-point at which outcomes were reported was discussed as part of protocol development, with the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				national audit. We have recently published this activity and outcomes from 2001 to 2016 in our SCTS Blue Book. This is a unique national audit of valve surgery including data on around 250,000 patients undergoing aortic, mitral and tricuspid valve surgery in the UK over the last 15 years. We are proud as professionals, and for the NHS, that survival has continued to improve over this time despite the patients being older and sicker. The NICE guidelines are a timely document and is published at a time that confidence in guidelines issued by The American College of Cardiology and European Society of Cardiology have become increasingly strained. In the cardiovascular device arena in particular, it has become apparent that research is frequently designed, funded and the findings interpreted by device companies in order to achieve regulatory approval. Serious concerns in the surgical community surround the following: 1. The use of primary end points favouring the percutaneous approaches. For example, in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) MitraClip trial, blood transfusion was included in the composite end point, weighted equally with mortality and stroke. 2. Reporting outcomes after relatively short follow-up to facilitate earlier regulatory approval, a strategy which favours the least invasive option and minimizes the opportunity to observe how incomplete or ineffective treatment affects long-term survival and quality of life. 3. The use of a non-inferiority trial design which makes it is easier (requires less efficacy and fewer patients) to show that outcomes are not significantly worse than to demonstrate that they are significantly better.	longest possible follow-up sought for outcomes such as mortality and quality of life and shorter time-point of 30 days for other outcomes where the aim was to identify more immediate procedural-related events, such as atrial fibrillation and major vascular complications. 3.The sample size for each outcome once studies have been pooled would be taken into account in the quality assessment process, as imprecision is one of the factors assessed using GRADE and is generally increased when sample sizes are smaller. 4.In terms of real-world data, it may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-interventions comparisons. However, it should be emphasised that randomised efficacy data present an idealised estimate of true effectiveness, and it is usually implausible that any differences

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				4. Many trials do not represent 'real world practice' with many patients excluded and yet findings are frequently extrapolated to a much wider population. This research is perceived then to unduly influence subsequent guidelines which tend to be written by clinicians who may have significant conflicts of interests. This introduces significant bias in the evidence base and undermines the confidence of both patients and clinicians. (Analysis of conflicts of interest among authors and researchers of European clinical guidelines in cardiovascular medicine. Jonathan Hinton, Thomas Reeves and Benoy Shah Clinical Medicine 2021 Vol 21, No 2: e166–70) In December 2019, The European Association for Cardio-Thoracic Surgery (EACTS) withdrew support from the 2018 EACTS-European Society of Cardiology (ESC) Clinical Guidelines for Myocardial Revascularization after an investigative news report, and subsequent clinical data which emerged raised questions about reported outcomes from the EXCEL trial (BMJ 2019;367:l7006 Surgical association withdraws support for stent advice after controversy over study) In February 2020 The Latin American Association of Cardiac and Endovascular Surgery (LACES) similarly withdrew support from the 2020 AHA/ACC guidelines for the management of heart valve disease, releasing the following statement after publication: 'Guidelines on management of cardiovascular disease are constructed based on the best clinical evidence. We believe the recently released AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease 2020 have important sections which fail on this major premise and therefore our association will not support them'.	between experimental and real-world settings would act to underestimate an intervention's 'true' effectiveness. Hence, preference will always be for high-quality randomised evidence when it comes to estimating the relative effects of different courses of action

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The full statement and rationale were published as referenced. (The Latin American Association of Cardiac and Endovascular Surgery statement regarding the recently released 2020 ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease Eur J Cardiothorac Surg 2021 Feb 12;ezab027. doi: 10.1093/ejcts/ezab027.) NICE is recognized internationally and nationally, across the whole profession and importantly by patients as having the highest standards in producing guidelines and so this publication is timely and will restore confidence in professionals and patients.	
Society for Cardiothoracic Surgery in Great Britain and Ireland	guideline	General	General	**IMPACT OF THE GUIDELINES ON PATIENTS** Since the draft recommendation SCTS has consulted widely with patients and groups representing patients with valve heart disease. The draft recommendations have been widely welcomed by patients. Patients have particularly highlighted the value of clarity about the following specific recommendations: 1. Management of patients with asymptomatic severe valve disease 2. Strong support for increasing access for minimally invasive valve surgery recognizing that patients may have to move to an experienced surgeon and centres when services are not available locally	Thank you for your comment.
Society for Cardiothoracic Surgery in Great	guideline	General	General	**Recognition of the impact of the Heart team in decision making** Multidisciplinary teams have become increasingly important in the management of heart valve disease. This document highlights complexities in the diagnosis, management (medical and intervention) and long term follow up of valve heart disease patients.	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Britain and Ireland				It is the view of SCTS that these decisions need to be taken within the setting of the multidisciplinary team. The MDT brings specialists together, usually within the setting of a multi-disciplinary meeting (MDM), with knowledge, skills and experience to interpret results, discuss diagnostic and therapeutic options, to help the patient decide on their preferred treatment. The recommendations made in these guidelines (e.g. Indications for intervention in patients with asymptomatic severe aortic stenosis,1.3.2 or Mitral valve repair for primary mitral valve regurgitation, 1.5.8) are most likely to be implemented in an MDM setting. The rapid evolution of virtual technology during the Covid 19 pandemic has facilitated much wider involvement of all clinicians in the network in the MDM process. In the future it may also allow for the involvement of patients and relatives either 'live' or in the form of records of video consultation bringing patients closer to the decisions made about them	added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Society for Cardiothoracic Surgery in Great Britain and Ireland	guideline	General	General	**Amalgamation of current national data sets into disease specific databases** The documents alluded to the presence of several national databases for heart valve intervention. The UK TAVI dataset and The National Adult Cardiac Surgery Audit data are the largest but there are other datasets for balloon valvuloplasty, edge to edge percutaneous therapies etc. There is an urgent need for these registries to be joined up as single registries covering intervention on specific valves e.g. an aortic valve intervention registry capturing all intervention on the aortic valve including, surgery, TAVI, valvuloplasty etc.	Thank you for your comment. NICE is unable to influence how these datasets are collected but we hope that the professional bodies will support your suggestion.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This will allow all professions and patients to audit outcomes in a much more meaningful way	
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	General	General	**Linkage of data to routinely collected NHS data for long term outcomes** Currently the many diverse national data audits administered either by National Institute for Cardiac Outcome Research or individual professional bodies are limited to data during hospital admission. Linkage of the data to routinely collected NHA data such as Primary Care Data, Health Episode Statistics data or Data from the National Death Registry. This means it's often difficult to get data on the impact of decision about diagnosis and treatment of valve disease across the patients and across the NHS as whole.	Thank you for your comment. We are unable to influence how these datasets are collected but we hope that the professional bodies will support your suggestion.
Society for Cardiothoracic Surgery in Great Britain and Ireland	Guideline	General	General	**Guidance on the length of the pathway for severe symptomatic disease** There are many patients who wait months on waiting lists for definitive treatment of severe symptomatic heart valve disease. Delaying definitive treatment increases the risks of deterioration of left ventricular function, heart failure, hospitalisation and death. There have been many reports of this occurring especially on TAVI waiting lists as increasing number of patients have been diverted to TAVI treatment. In the NHS there are several examples where there are national guidelines in place to limit the time taken form referral to diagnosis and diagnosis to intervention. Management of patients presenting with red flag symptoms of cancer would be such an example.	Thank you for your comment. We have included referral times in the relevant recommendations in sections 1.1 and 1.4. The length of the entire pathway from diagnosis to treatment varies due to a large number of factors and it is was not possible for the committee to make a consensus recommendation.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				SCTS wonders if this may be an opportunity to provide guidance on the length of the pathway for patients with severe symptomatic heart valve disease.	
St George's University Hospitals NHS Foundation Trust	Economic Model			The economic model overestimates the rates of vascular complication, stroke and new pacemaker requirements compared to current clinical practice in high and intermediate risk patients. At our institution in 2020 rates were 1.7%, 2.5% and 9.1% respectively. Furthermore 30-day and 1-year TAVI outcomes of nonagenarians are less favourable to lower age groups, with patients aged 70-79 the most favourable as demonstrated from data collected in the Swiss TAVI registry. (Attinger et al, 2020) This strengthens the case of a likely bias against TAVI given the majority of RCT data has been collected in older patients.	Thank you for your comment. We edited the model to use baseline risks coming from published NICOR data which reflects UK clinical practice. Rates of vascular complication, stroke and new pacemaker requirement are now: 2.1%, 2.3% and 9.7%, which are reasonably close to the figures provided by your institution. The treatment effects used in the model were calculated from a meta-analysis including the most recent trials on TAVI (PARTNER 2, PARTNER 3 and Evolut). We noted a trend where more recent trials enrolled younger people e.g., Evolut and PARTNER 3 with, respectively, 73 and 74 years old. We propose that an important part of the treatment effects of the model is now estimated using trials on younger patients.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
St George's University Hospitals NHS Foundation Trust	Economic Model	026	021	The procedural costs used here are inaccurate as they use historic data based on extreme and high risk patients in the TAVI group versus low risk patients in the SAVR group.	Thank you for your comment. The procedural cost for high and intermediate TAVI patients are now taken from the currency code EY21B relative to TAVI with CC score 0-7. This HRG reflects the cost of lower risk patients if compared with the currency code EY21A which instead reflects the cost of very high risk and inoperable patients. Therefore, a TAVI intervention will have the same cost (EY21B) regardless of the risk-level, as recommended by the committee. However, the cost of surgery is still differentiated according to the surgical risk of the patients.
St George's University	Economic Model	027	012	This data is not applicable to contemporary UK practise: at our centre patients are now discharged directly to a monitored ward bed and ICU is no longer used outside of the context of a rare complication. We have recently started a low risk pathway in which selected patients are treated as a day case procedure.	Thank you for your comment. After further discussion the committee, agreed to use UK data for length of hospital stay and ICU stay

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Hospitals NHS Foundation Trust					as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. Hospital LOS ranges by surgical risk group from 3 to 3.3 in TAVI. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
St George's University Hospitals NHS Foundation Trust	Economic Model	029	010	The cost effectiveness data is flawed due to incorrect data and incorrect models.	Thank you for your comment. We revised the model to better reflect UK clinical practice and account for the comments received by stakeholders. The model and the cost-effectiveness analysis now reflects UK practice and contemporary outcomes. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).
St George's University Hospitals NHS Foundation Trust	Economic Model	033	001	Biventricular pacing should be removed from the weighted average it does not relate to TAVI which does not induce heart failure.	Thank you for your comment. We have now removed biventricular pacing from the calculation of pacemaker cost. Moreover, in the base case scenario, all the costs are assumed to be included in the hospital stay cost (HRGs) so they are now only costed separately in a sensitivity analysis.
St George's University Hospitals NHS Foundation Trust	Economic Model	042	019	The most recent randomised data point to a lower risk of stroke following TAVI as compared with SAVR, lower rates of permanent pacemaker implantation and lower rates of paravalvular leak due to iterative improvements in technology. (PARTNER 3 trial) Therefore this economic model should be revised with contemporary rather than historic data. Conversely risks of new onset atrial fibrillation have been shown to be higher post SAVR and the associated monetary and quality of life costs are not included in this analysis. Transapical access has largely been abandoned and this should be reflected in the model.	Thank you for your comment. The treatment effects in the model have been updated with Popma 2019 (Evolut trial) and Leon 2021 (Partner 3) to reflect recent evidence. Following further discussion of the health economics subgroup and the full committee it was decided to use in the base case scenario only the trials on second and third generation valves

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					(Evolut, PARTNER 2 and PARTNER 3). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
St George's University Hospitals NHS Foundation Trust	Economic Model	048	008 - 009	The entire economic model is flawed due to the use of historic paravalvular leak rates and effects on mortality. This has been addressed by improvements in TAVI valve design which are not reflected in this model	Thank you for your comment. We edited TAVI baseline PVL rates to address the recent improvement in TAVI valve. The new evidence used (Howard 2016) reports PVL rates with a Sapien 3 valve (3rd generation) and it is in line with the latest data reported in the BCIS TAVI audit.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
St George's University Hospitals NHS Foundation Trust	Guideline	008	007	We are concerned that this guideline is biased towards surgery as the only treatment option for patients with asymptomatic severe aortic stenosis as no mention of TAVI is made here. We would suggest the word intervention rather than surgery.	Thank you for your comment. We have made the edit you suggest. We revised the economic model based on stakeholder comments. We have changed the recommendations and TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
St George's University Hospitals NHS Foundation Trust	Guideline	011	005	There is no guidance on referral to treatment times, what constitutes an acceptable timescale for treatment and how this should be managed in already overwhelmed services. In our experience patients can face delays to eventual treatment and in the interim can develop decompensated heart failure requiring prolonged hospital admissions with vastly increased costs. Approximately a quarter of our TAVI cases are undertaken for these decompensated patients who often have a higher burden of left ventricular impairment and renal failure. This will be exacerbated during the COVID pandemic and the costs in treating these patients are likely to be significant. Currently a single point of referral is widely being adopted for aortic valve disease. Suggesting a surgical referral in the first instance will delay eventual treatment if surgery is not recommended.	Thank you for your comment. The guideline committee were unable to recommend referral to treatment times as this would be highly variable dependent upon clinical and patient factors and therefore a consensus recommendation could not be made on time scales. The recommendation 1.5.1 is for people with an indication for surgery. Although we acknowledge that some of these people will not undergo surgery this option needs to be discussed within the context of shared decision making.
St George's University Hospitals NHS	Guideline	011	010	No mention is made of TAVI in this section despite it being the modality of choice for patients at high and intermediate risk aortic stenosis. We feel patients should be made aware of all treatment options available and avoiding discussion is heavily biased against TAVI.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation Trust					for people at intermediate or low surgical risk (1.5.3). We now therefore refer to transcatheter in the bullet point in recommendation 1.5.1 on type of access. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
St George's University Hospitals NHS Foundation Trust	Guideline	012	003 - 005	We are concerned that restricting TAVI to patients who are unsuitable for SAVR will result in patients undergoing an unnecessarily invasive operation with a higher death and stroke rate, a higher rate of new-onset atrial fibrillation, a longer length of hospital stay and a higher level of post-operative pain based on the most contemporary meta-analysis of randomised controlled trials comparing TAVI to SAVR amongst all risk categories. (Siontis et al, 2019) This recommendation will be challenging to change in practise as would differ significantly from current UK, European and North American professional society clinical guidelines. We are also concerned that this draft guideline is not patient focussed and does not take into account more holistic influences on decision making such as caring roles for family members or other commitments which would lead to a decision to choose a TAVI over valve longevity uncertainty. Furthermore quality of life assessments have not been considered ignoring the impact of frailty, cognition and comorbidities such as intervention in aortic stenosis ahead of cancer treatments. These factors are all routinely explored in the highly specialised Heart Team discussions which currently	Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). The evidence reviewed included outcomes of mortality, quality of life, stroke, atrial fibrillation and hospital length of stay highlighted in your comment, which were discussed alongside cost-effectiveness analysis, but postoperative pain was not included as an outcome in the protocol. Recommendations under 'decisions about interventions' emphasise the importance of shared decision

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				form the basis of all treatment of patients with severe aortic stenosis in our institution which is an approach backed by consensus of all other national and international guidelines and we would advocate to continue for the benefit of our patients. (Valve for life, NHS plan, BCIS, GIRFT, ESC, AHA). The underlying rationale for this guidance is based on a flawed economic analysis using historic data using now retired early generation TAVI systems and do not pertain to current practice. Current TAVI devices and implantation techniques result in less paravalvar leak and less permanent pacemaker implantation, with our last local audit of 2020 data showing a permanent pacemaker rate half of that 2017. At our institution, the vast majority of patients are now discharged directly to a monitored ward bed and are then discharged home within 48 hours. ICU use is rare following TAVI. Innovation during the COVID pandemic has led to the recent introduction of a low risk pathway, where selected patients are now treated as a day-case procedure. These developments have will have a significant beneficial impact on cost and also patient decision making which is not reflected in this guideline. There has been no attempt to risk stratify and this makes a blanket recommendation meaningless. I have authored a comprehensive review on the indications for TAVI vs Surgical AVR for the online publication UpToDate which is heavily referenced and peer-reviewed : I reproduce below the data I analysed : **TAVI versus SAVR** — While individual trials comparing TAVI versus SAVR have targeted specific surgical risk groups, meta-analyses have pooled	making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. We have revised the economic model to reflect contemporary TAVI outcomes and costs (including ICU and LOS) and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve price for people at

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				these groups to examine pooled outcomes and subgroup differences. A meta-analysis included four trials (the largest trial with 2032 intermediate-risk patients, two studies with 699 and 795 high-risk patients, and one study with 280 low-risk patients) to assess outcomes at two years [Ref available]. **With high surgical risk** — In the above described meta-analysis in which nearly all patients had intermediate to high surgical risk, transfemoral TAVI (but not transthoracic TAVI) was associated with lower mortality than SAVR [Ref]. The meta-analysis included the following two pivotal trials in patients with high surgical risk: In both trials, major vascular complications were more frequent after TAVI, and major bleeding and new-onset atrial fibrillation were more frequent after SAVR. Since data are not convincing that outcomes are different with different types of transcatheter heart valves, TAVI (with either balloon expandable or self-expanding valve) is recommended for high-risk patients who are candidates for a transfemoral approach. (See 'Symptomatic patients' above.) **In intermediate-risk patients** — Randomized trials in patients with severe AS with intermediate surgical risk have found similar rates of death or disabling stroke following TAVI and SAVR [23,24] as summarized by the following meta-analyses: Limitations of studies included in these meta-analyses include use of transcatheter valves that are no longer in use (and cause higher rates of paravalvular aortic regurgitation than current models), use of transthoracic access routes that are now used less commonly than the subclavian/axillary approach, use of only bioprosthetic valves for SAVR in the included randomized trials, and limited duration of follow-up. In	intermediate or low surgical risk (1.5.3). See evidence review H. NICE and NHSEI have published a joint implementation strategy alongside the guideline. Patient choice cannot justify the use of a non-cost-effective procedure, as allocating NHS funding to a particular technology, means that patients in other areas would have to be denied effective treatments. Stratification by risk in treatment effects was initially proposed but could not be done due to methodological issues. In the revised version of the model, treatment effects have been updated to draw data from trials evaluating only 2nd and 3rd generation valves. As no trial has been conducted on high-risk people using modern valves, a stratification could not be conducted as it would have led to the exclusion of high risk,

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				addition, in the second meta-analysis, the transthoracic component of the meta-analysis pooled data from the STACCATO trial (comparing transapical TAVI with SAVR) with the transthoracic subgroup of the PARTNER 2A trial. Limitations of the STACCATO trial include use of transapical access, which is a less common route, lack of preprocedural multidetector computed tomography (unlike PARTNER 2A and current clinical practice), the device success rate was unusually low (79 percent) compared with rates seen in higher-risk patients, and the rate of adverse events was unusually high, which triggered early termination of the study [28]. The largest trial included in both meta-analyses is the PARTNER 2A trial, which randomly assigned 2032 intermediate-risk patients (mean STS-PROM score of 5.8; mean age 82 years) with severe AS to undergo either TAVI (with the SAPIEN-XT balloon-expandable valve, which is no longer implanted) or SAVR with two-year follow-up [23]; a study published after these meta-analyses reported five-year outcomes [30]. Patients were divided into two cohorts prior to randomization on the basis of an evaluation of the peripheral arteries: 76.3 percent were included in the transfemoral-access cohort and 23.7 percent were included in the transthoracic-access (transapical or transaortic) cohort. A meta-analysis comparing TAVI and SAVR in patients with severe AS with predominantly intermediate surgical risk found similar mortality rates at 30 days (3.0 versus 3.0 percent; relative risk [RR] 1.03; 95% CI 0.71-1.48), one year (9.6 versus 9.6 percent; RR 1.01; 95% CI 0.08-1.28) and ≥2 years (14.2 versus 13.5 percent; RR 1.01; 95% CI 0.62-1.66) in the two treatment groups (data shown based upon analysis in randomized trials) [25]. In analyses that included observational studies as well as randomized trials, the point estimate for stroke suggested a benefit for TAVI compared with SAVR but the confidence	a group extremely important to assess given their substantial surgical cost and loss of quality of life after the intervention. Although treatment effects were ultimately not stratified, stratification by risk was conducted for the following parameters: • Cost and resource usage • Mortality in the long and short term • Utility values Therefore, we believe that the model still offers differential results for each category as cost, mortality and utility are arguably the main features differentiating people at different surgical risk.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				interval overlapped no effect at 30 days, one year, and ≥2 years (total stroke events 5.7 versus 6.4 percent; RR 0.92; 95% CI 0.80-1.05). This meta-analysis did not examine the relationship between access site and outcomes. ● A separate meta-analysis of four randomized trials with 3179 patients with severe AS at predominantly intermediate risk of perioperative death examined the effect of TAVI versus SAVR on outcomes at median follow-up of two years [26]. The included trials were the PARTNER 2A, US Pivotal, NOTION, and STACCATO trials [20,23,27,28]. Baseline risk estimates were derived from a systematic review of observational studies of bioprosthetic SAVR [29]. ● Transfemoral TAVI compared with SAVR resulted in reduced mortality (HR 0.79, 95% CI 0.88-0.94; 30 fewer per 1000 patients) and reduced acute kidney injury (RR 0.38, 95% CI 0.27-0.53, 53 fewer per 1000 patients). The point estimate for stroke also suggested a benefit for transfemoral TAVI compared with SAVR but the confidence interval overlapped no effect (RR 0.80, 95% CI 0.61-1.01, 20 fewer per 1000 patients). • TAVI compared with SAVR resulted in reduced atrial fibrillation and major bleeding, with greater reductions in bleeding among patients undergoing transfemoral TAVI versus transapical TAVI. • In contrast, TAVI compared with SAVR resulted in more frequent worsened symptoms of heart failure (one point worse on the NYHA scale; odds ratio [OR] 1.29, 95% CI 1.08-1.55, 59 more per 1000 patients), aortic valve re-intervention (RR 3.25; 95% CI 1.29- 8.14, 7 more per 1000 patients), permanent pacemaker insertion (RR 2.45, 95% CI 1.17-5.14, 134 more per 1000 patients), and moderate or severe aortic valve regurgitation (RR 12.22, 95% CI 5.17-28.88, 80 more per 1000 patients). • For alternative (nontransfemoral) access TAVI compared with SAVR, the point estimates suggested increased mortality (HR 1.34, 95% CI 0.91-1.97, 57 more per	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1000 patients) and stroke (HR 1.67, 95% CI 0.97-2.87, 45 more per 1000) but the confidence intervals overlapped with no effect. Additional data on outcomes in intermediate surgical risk patients were provided by the SURTAVI trial (included in the first meta-analysis described above but not the second one), which randomly assigned 1746 patients with symptomatic severe AS with intermediate surgical risk (mean STS-PROM 4.5 percent) to TAVI (with a self-expanding bioprosthesis: CoreValve in 84 percent and Evolut R in 16 percent) or SAVR; 1660 patients underwent attempted SAVR or TAVI [24]. Nearly all of the TAVI procedures (93.6 percent) were performed via iliofemoral access. An observational study using a propensity score analysis suggested that TAVI with a balloon-expandable SAPIEN XT valve may be superior to SAVR for intermediate-risk patients, but it is possible that residual confounders influenced the results [31]. In low-risk symptomatic patients — The efficacy and safety of TAVI in patients with AS with low estimated surgical risk were evaluated by the following randomized trials [32,33]: In the transfemoral-access cohort, TAVI resulted in a lower event rate than SAVR at two years (16.8 and 20.4 percent; HR 0.79; 95% CI 0.62-1.00); however, at five years, event rates were similar (44.5 versus 42.0 percent; HR 1.02; 95% CI 0.87-1.20). - In the transthoracic-access cohort, outcomes were similar in the TAVI and SAVR groups at two years (27.7 and 23.4 percent; HR 1.21; 95% CI 0.79-1.65); in contrast, at five years, events rates were higher with TAVI (59.3 versus 48.3 percent; hazard ratio, 1.32; 95% CI 1.02-1.71). - Improvement in health status at five years was similar in the TAVI and SAVR groups (NYHA functional class I or II in 89 and 92.7 percent). • A late benefit of SAVR compared with TAVI was lower rates of repeat	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				hospitalizations (25.2 versus 33.3 percent) at five years [30] and lower rates of at least mild paravalvular AR (6.3 versus 33.3 percent). • Rates of aortic valve reinterventions at five years were lower after SAVR (0.8 versus 3.2 percent) [30]. However, reinterventions after TAVI were due to progressive stenosis or regurgitation, and nearly all (18 of 21) were treated with either TAVR or balloon valvuloplasty; in-hospital mortality from valve reintervention was 5 percent (1 of 21 patients). In contrast, reinterventions after SAVR were largely due to endocarditis (four of six cases), and most were treated with repeat surgery; in-hospital mortality was 50 percent (three of six patients). • Of note, these data are not sufficient to compare the long-term risk of endocarditis after TAVI and SAVR. The risk of endocarditis after TAVI and SAVR is discussed separately. (See "Prosthetic valve endocarditis: Epidemiology, clinical manifestations, and diagnosis" and "Transcatheter aortic valve implantation: Complications".) The incidence of the primary composite end point of death from any cause or disabling stroke at 24 months was similar in the TAVI and SAVR groups (12.6 and 14.0 percent). ● NYHA symptoms and quality of life (measured by the Kansas City Cardiomyopathy Questionnaire [KCCQ] summary score) improved significantly in both groups through 24 months of follow-up. At one month, there was a higher proportion of patients with an improved KCCQ summary score at one month in the TAVI group compared with the SAVR group. ● The SAVR treatment group experienced significantly higher 30-day rates of acute kidney injury (4.4 versus 1.7 percent), atrial fibrillation (43.4 versus 12.9 percent), and transfusion requirement (41.1 versus 12.6). The TAVI group experienced significantly higher 30-day rates of major vascular complications (6.0 versus 1.1 percent) and need for permanent pacemaker implantation (25.9 versus 6.6	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				percent). Moderate or severe paravalvular aortic regurgitation was more common at one year in the TAVR group (5.3 versus 0.6 percent in the SAVR group). Mean prosthetic valve gradients were significantly lower and prosthetic aortic valve areas were higher in the TAVI group. **Low Risk** The efficacy and safety of TAVI in patients with AS with low estimated surgical risk were evaluated by the following randomized trials [32,33]: In the transfemoral-access cohort, TAVI resulted in a lower event rate than SAVR at two years (16.8 and 20.4 percent; HR 0.79; 95% CI 0.62-1.00); however, at five years, event rates were similar (44.5 versus 42.0 percent; HR 1.02; 95% CI 0.87-1.20). - In the transthoracic-access cohort, outcomes were similar in the TAVI and SAVR groups at two years (27.7 and 23.4 percent; HR 1.21; 95% CI 0.79-1.65); in contrast, at five years, events rates were higher with TAVI (59.3 versus 48.3 percent; hazard ratio, 1.32; 95% CI 1.02-1.71). - Improvement in health status at five years was similar in the TAVI and SAVR groups (NYHA functional class I or II in 89 and 92.7 percent). • A late benefit of SAVR compared with TAVI was lower rates of repeat hospitalizations (25.2 versus 33.3 percent) at five years [30] and lower rates of at least mild paravalvular AR (6.3 versus 33.3 percent). • Rates of aortic valve reinterventions at five years were lower after SAVR (0.8 versus 3.2 percent) [30]. However, reinterventions after TAVI were due to progressive stenosis or regurgitation, and nearly all (18 of 21) were treated with either TAVR or balloon valvuloplasty; in-hospital mortality from valve reintervention was 5 percent (1 of 21 patients). In contrast, reinterventions after SAVR were largely due to endocarditis (four of six cases), and most were treated with repeat surgery; in-hospital mortality	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				was 50 percent (three of six patients). • Of note, these data are not sufficient to compare the long-term risk of endocarditis after TAVI and SAVR. The risk of endocarditis after TAVI and SAVR is discussed separately. The incidence of the primary composite end point of death from any cause or disabling stroke at 24 months was similar in the TAVI and SAVR groups (12.6 and 14.0 percent). ● NYHA symptoms and quality of life (measured by the Kansas City Cardiomyopathy Questionnaire [KCCQ] summary score) improved significantly in both groups through 24 months of follow-up. At one month, there was a higher proportion of patients with an improved KCCQ summary score at one month in the TAVI group compared with the SAVR group. ● The SAVR treatment group experienced significantly higher 30-day rates of acute kidney injury (4.4 versus 1.7 percent), atrial fibrillation (43.4 versus 12.9 percent), and transfusion requirement (41.1 versus 12.6). The TAVI group experienced significantly higher 30-day rates of major vascular complications (6.0 versus 1.1 percent) and need for permanent pacemaker implantation (25.9 versus 6.6 percent). Moderate or severe paravalvular aortic regurgitation was more common at one year in the TAVR group (5.3 versus 0.6 percent in the SAVR group). Mean prosthetic valve gradients were significantly lower and prosthetic aortic valve areas were higher in the TAVI group. ● In the Evolut Low Risk trial, 1468 patients (mean age 74) with severe AS and low surgical risk (mean STS-PROM 1.9±0.7) were randomly assigned to TAVI with a self-expanding valve or surgical aortic valve replacement; a total of 1403 patients underwent the assigned procedure [32]. Nearly all TAVI procedures were performed via transfemoral access (99 percent). ● The estimated incidence of the primary endpoint (a composite of death or disabling stroke at two years) was 5.3 percent in the TAVI group and 6.7	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				percent in the surgery group (absolute difference, 1.4 percentage points; 95% credible interval for difference, -4.9 to 2.1). Thus, the noninferiority threshold was met. • At 30 days, the TAVI group had significantly lower incidences of disabling stroke (0.5 versus 1.7 percent), bleeding complications (2.4 versus 7.5 percent), acute kidney injury (0.9 versus 2.8 percent), and atrial fibrillation (7.7 versus 35.4 percent) but higher rates of moderate or severe aortic regurgitation (3.5 versus 0.5 percent) and permanent pacemaker implantation (17.4 versus 6.1 percent). Mortality rates were not significantly different (0.5 versus 1.3 percent). • At one year, hospitalizations for HF were significantly less frequent in the TAVI group (3.2 versus 6.5 percent) and prosthetic aortic valve gradients were significantly lower (8.6 mmHg versus 11.2 mmHg) than in the surgery group. Mortality rates at one year were similar in the two groups (2.4 versus 3.0 percent). •There were differences in patient populations as well as composite endpoints between the Evolut Low Risk (self-expanding valve) and PARTNER 3 (balloon-expandable valve) trials. In the PARTNER 3 trial, a greater proportion of screened patients were excluded for risk factors such as severe left ventricular outflow tract calcium, adverse aortic root (small sinus of Valsalva or small, calcified sinotubular junction) and poor transfemoral access; these exclusions may have contributed to the low rates of TAVI complications such as need for permanent pacemaker insertion and paravalvular regurgitation in this trial. The PARTNER 3 trial included rehospitalization at one year in the composite endpoint but the Evolut Low Risk trial did not. Since the Evolut Low Risk trial reported a reduction in hospitalizations for HF at one year, overall outcomes for TAVI with a self-expanding valve and TAVI with a balloon-expandable valve are likely to be similar. Further study is required to determine long-term	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				outcomes. (See 'Transcatheter valve type' below.) Data from registries — Additional information on outcomes following TAVI come from registry studies. Reports from the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) registry, the United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) registry, and the German Aortic Valve Registry (GARY) have included the following outcome data for patients with intermediate to high median risk (ie, STS-PROM 7.1 [34], 5 [35], or logistic Euroscore 18.5 [36,37]): In the UK TAVI registry, stroke within 30 days of TAVI was the only independent procedural predictor of mortality at three and five years [36]. Independent predictors of three-year mortality were renal dysfunction, atrial fibrillation, respiratory dysfunction, and ventricular dysfunction. Coronary artery disease and age were independent predictors of mortality at five years. Device type, access route, and paravalvular leak did not independently predict long-term outcome. A study of 241 patients (mean age 79 years) from the UK TAVI registry found that 91 percent of patients were free of structural valve degeneration at 5 to 10 (median 5.8)-year echocardiographic follow-up [38]. There was one case of new severe aortic regurgitation at 5.3 years, 12 cases of moderate aortic regurgitation, and nine cases of moderate restenosis. Subgroup differences By access site — As described above, patients undergoing transfemoral TAVI have better outcomes than patients undergoing alternative (nontransfemoral) access TAVI, as indicated by subgroup analyses of meta-analyses and individual trials. As an example, a meta-analysis of 27 observational studies and one randomized trial with a total of 17,020 patients undergoing TAVI found that 30-day mortality was 4.7 percent with the transfemoral approach and 8.1 percent with an alternative approach [39]. One-year mortality was 16.4 percent with transfemoral access and 24.8 percent with	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				nontransfemoral access. Transfemoral access was associated with a higher rate of vascular complications (OR 2.1; 95% CI 1.48-2.99) but a lower rate of surgical conversion (OR 0.59; 95% CI 0.42-0.81), while rates of bleeding and cerebrovascular events were similar to those with alternative access. However, the available data are not adequate to determine how much of the excess mortality seen in patients undergoing alternative access TAVI is caused by the alternative access procedure and how much is caused by excess comorbidity associated with the need for alternative access. Sex-specific differences — Although women experience more major bleeding and vascular complications, female sex is an independent predictor of lower one-year mortality after TAVI. Thus, sex-specific mortality risk following TAVI is opposite of that following SAVR, for which women have higher mortality risk than men. We suggest including female sex as a factor when weighing the potential risks and benefits of TAVI versus SAVR, since the data suggest that TAVI is superior to SAVR for women with high-risk symptomatic AS. In the PARTNER 3 trial, 1000 patients (mean age 73) with severe AS and low surgical risk (mean STS-PROM 1.9±0.7) were randomly assigned to TAVI with a balloon-expandable valve or surgical aortic valve replacement; 950 patients received the assigned procedure [33]. Inclusion criteria included eligibility for transfemoral access for the TAVI procedure. ● The estimated incidence of the primary endpoint (a composite of death, stroke, or rehospitalization at one year) was significantly lower in the TAVI group than in the surgical group (8.5 versus 15.1 percent; absolute difference, -6.6 percentage points; 95% CI -10.8 to -2.5). Thus, both noninferiority and superiority criteria were met. • At 30 days, TAVI resulted in lower rates of stroke (0.6 versus 2.4 percent) and new-onset atrial fibrillation (5 versus 39.5 percent) and there	

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				were no significant differences in the frequency of permanent pacemaker insertions (6.6 versus 4.1 percent) or moderate or severe paravalvular regurgitation (0.8 versus 0.0). Mortality rates were not significantly different (0.4 versus 1.1 percent). • At one year, prosthetic valve mean gradients (13.7 versus 11.6) and frequency of moderate or severe paravalvular regurgitation (0.6 versus 0.5 percent) were similar in the TAVI and surgery groups. Mortality rates were similar in the two groups (1.0 and 2.5 percent). **I AM HAPPY TO SUPPLY THE FULL PAPER ON THE ABOVE FOR REVIEW BY NICE ON REQUEST**	
St George's University Hospitals NHS Foundation Trust	Guideline	012	006	This recommendation would be a challenging change in practise. We currently treat bicuspid aortic stenosis in patients felt appropriate by the Heart Team with good results. Our strategy is supported by registry data (Forrest 2020) and the alternative would be palliative care.	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely currently, meaning evidence should not be extrapolated.
Swansea Bay University Health Board	Comments table	General	General	Questions 1 and 2. Wales has the oldest population in the UK with 11.7% of the population being 85 years or older at the last census in 2011 (5.5% in the rest of the UK). We currently treat patients 80 years and over, or patients less than 80 with significant co-morbidity as assessed by the Heart Team with TAVI. If we are to treat this group of patients with AS with SAVR as "first line treatment", this will have significant implications with the need	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to increase capacity in the whole cardiac surgical pathway which will not currently be possible. Urgent specialist review or echo within 4 weeks for patients within the Mid and South West Wales region is currently not possible due to a shortage of echo-trained cardiac physiologists and a shortage of secondary care cardiologists. Minimally invasive aortic surgery is currently only provided by 2 cardiac surgeons in the whole of Wales. If patients are to be referred to another centre for minimally invasive AVR this will require referral to NHS providers at high cost. Question 4. During the Covid pandemic in our centre, the majority of patients waiting for surgical aortic valve replacement were diverted to a TAVI pathway due to the need for ventilation, post-operative ICU stay, longer hospital stay and the larger resource utilisation required for cardiac surgery. The Covid pandemic has accelerated the evolution of the TAVI pathway in achieving shorter referral to treatment times (9 week median), shorter lengths of stay (1.6 days median all comers), minimised resource utilisation whilst achieving excellent outcomes (1.3% 30 day mortality, 0.6% stroke, no VARC 2 major vascular complications, 7.6% pacemaker rate).	comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The committee acknowledged that there may be challenges to the implementation of these recommendations. However, they sought to recommend those tests and interventions which were the most clinically and cost effective. Your comments will be considered by NICE where relevant support activity is being planned. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Swansea Bay University Health Board	Economic Report - TAVI	General	General	We believe that the TAVI Economic Model represents the most flawed element of the Draft Guideline. The principal problem with the Economic model is that is constructed using data drawn from old trials of TAVI versus surgery, which are not reflective of current clinical practice, and hence costs, as well as outcomes and their associated costs, are grossly inaccurate, leading to grossly inaccurate assessment of cost-effectiveness. In addition, the costs of the TAVI procedure are significantly overestimated, and are not representative of current NHS TAVI costs.	Thank you for your comment. The model has been revised following the Stakeholder comment and, in its current state, it uses only treatment effects coming from 2nd and 3rd generation valves. Costs were also updated to reflect the UK practice and are taken from UK NHS sources only: UK TAVI trial for Length of hospital stay and ICU stay, NHS Reference Costs 2018-2019 for the cost of the procedure and NHS Supply Chain for the average price of a TAVI valve. We think that, in the current state, the model is accurately

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					reflecting the cost of a TAVI procedure in the UK. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Economic report TAVI	007	016	It is inappropriate to exclude low-risk patients in the Economic model. The most contemporaneous data comparing TAVI and surgery are in low-risk patients. Older low-risk patients already routinely undergo TAVI in the UK (e.g. healthy patients aged 80 or older). The Economic model should be revised to include low-risk patients.	Thank you for your comment. The committee agreed to include low-risk patients which were added in the economic model and assumed to be, on average, 75 years old. Cost-effectiveness is assessed for this category of people as well. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Economic report TAVI	007 009 013	018 2.2.1.2 014 - 022	The Economic model has worked on a Lifetime horizon, and has subsequently based this on a 30-year time-frame, as well as a 'shorter' 13-year time-frame. It is inappropriate to base the model on such a long-term timeframe for the following reasons:- 1. There are no RCT data comparing TAVI and surgery beyond 5 years. The economic model was therefore based on estimation of events, rather than real data. 2. The average age of a patient undergoing TAVI in the NHS is 81 years. The average life-expectancy of patients undergoing TAVI is therefore far less than 13 years, let alone 30 years.	Thank you for your comment. The committee agreed to reduce the time-horizon in the base case scenario to 15 years. This should reflect the average life expectancy of 75 years old TAVI patients, who now populate the low surgical risk category. A period shorter than 15 years was considered inappropriate as some of the consequences of TAVI, such as the higher need of reintervention, would occur later. Nevertheless, several scenario analyses were conducted presenting the cost-effectiveness results using

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					different time horizons: 5, 10, 15 and 30 years.
Swansea Bay University Health Board	Economic report TAVI	012	018 - 020	The Economic model is based on the same data as the Evidence Review. This is inappropriate for the Economic model for the same reasons outlined above. Specifically:- 1. The data are dominated by older trials which, as described above, are not consistent with current practice, or current outcomes, from TAVI in the UK. As a result, the outcome data and associated costs are not representative of current practice. 2. The data from the UK TAVI trial are not included, and would strengthen the model significantly by representing UK-based data, as well as more contemporary data 3. The data from the Evolut Low Risk trial are not included in the Economic model. 4. Readily available UK-specific data on outcomes and costs of TAVI in the UK from the UK TAVI database have not been used, although they are available in the public domain (www.bcis.org.uk) 5. There is no weighting for more contemporary studies despite the fact that these are far more reflective of current UK practice, as outlined in detail above. 6. Data with trans-apical access should not be included in the Economic model, since trans-apical access is more expensive, has worse outcomes, and is only used in 1.3% of patients in the UK	Thank you for your comment. 1. The committee agreed that the model should be based on recent rather than historical data to account for valve efficiency and technological improvement. Therefore, in the base case scenario, treatment effects are calculated using only trials of 2nd and 3rd generation valves: PARTNER 2, PARTNER 3 and Evolut. 2. UK TAVI trial is still unpublished and its effectiveness findings could not be included in the meta-analysis Descriptive statistics data from the trial were used to inform length of hospital stay and ICU days after TAVI and SAVR as those reflect UK practice.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					3. The Evolut low risk trial has been added to the meta-analysis 4. TAVI outcomes (baseline risks) are now taken from the latest BCIS UK TAVI audit. 5. Only contemporary studies (2nd or 3rd generation valves) are now used in the model and so weighting is no longer applicable 6. The trials used to inform the meta-analysis are now predominantly using the transfemoral approach. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Economic report TAVI	014	Table	The rate of moderate/severe PVL for TAVI used is 4.63%. This is based on data from old trials with obsolete valve types. In our unit we had zero moderate or severe PVL in 2010 and 1.2% moderate PVL (no severe) in 2019.	Thank you for your comment. We updated our data for PVL to reflect the outcomes of new generation valves (SAPIEN 3). The new rate we use for moderate and severe PVL is 2.7%, which is very close to the percentage reported in the last BCIS audit for TAVI in 2019/20 for moderate and severe PVL (3%). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Economic report TAVI	014	Table 016 - 006	The re-intervention rate for surgery is based on a single registry study which is relatively small in size (<1000 patients), and which includes data on valves which are no longer in use and which had high rates of re-intervention, specifically the Mitroflow. This constitutes very poor evidence on which to base an important element of the economic model	Thank you for your comment. The paper from Rodriguez-Gabella was chosen to inform the baseline risk of reintervention after SAVR as it was the only one with a follow-up covering most of the time horizon of the model (13 years last follow up). Since, the rate of reintervention increases significantly over time the length of follow-up is crucial. Using other data would have involved relying more on extrapolation. We are aware that efficiency improvements and new valves may have reduce the rate of re-intervention but looking at UK data, it does not seem that the model is over-estimating the number of reinterventions after surgery, at least in the short term. UK TAVI trial: 2.9% NICE model: 1.4%

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Swansea Bay University Health Board	Economic report TAVI	015 021 - 022	Table	The relative re-intervention rate for TAVI and surgery is flawed and has a significant effect on costs. It is based on a paper (Ler (2020) that was excluded from the Evidence Review in this same Draft Recommendation. In Evidence Review 8, Appendix I (https://www.nice.org.uk/guidance/gid-ng10122/documents/evidence-review-8) NICE state that they excluded Ler (2020) on the grounds that 'methods are not adequate/unclear'. 12 month valve re-intervention rates post TAVI in our unit in 2020 was zero and 0.8% in 2019.	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review which did not meet the review protocol criteria (see appendix A in evidence review H), though it was included as an evidence for the model. After further discussion the committee agreed to exclude this evidence as it was clearly focused on old generation valves. Relative treatment effects for reintervention now come from the trials included in the literature review as these were fully discussed and reviewed by the committee. In the base case we are now only using the treatment effect captured in trials evaluating 2nd and 3rd generation valves and there is a sensitivity analysis where this figure is instead calculated from trials of 3rd generation valves only.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Economic report TAVI	016	Table - costs	The data used on costs of ICU stay for TAVI are inappropriate. The model has based costs on an average ICU stay of 2 days for intermediate risk patients, and 3 days for high-risk. The average number of days on ICU for TAVI in our unit are zero for intermediate risk and zero for high-risk. In 2020 only 1 patient (0.6% of TAVI patients) required an ITU stay. This has led to a major overestimation of the costs of the TAVI procedure.	Thank you for your comment. After further discussion the committee agreed to use UK data for length of hospital stay and ICU stay as it appears clear that the practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					these numbers were then adjusted for the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Economic report TAVI	017	Table - costs	The data used for Total Length of Stay are inappropriate. The model uses a LOS of 6 and 8 days for TAVI in intermediate and high risk respectively vs 9 and 11 days for surgery. All comers data from our unit show median LOS 1.6 days, mean LOS 2.0 days for TAVI and 9 days median, 12.7 day mean LOS for SAVR in 2019/20 pre-Covid. This has further contributed to overestimation of the costs of the TAVI procedure. The Economic Model has based procedural cost for TAVI on NHS Reference costs, £9658 for intermediate-risk and £11979 for high-risk. It would be more appropriate to base procedure costs on the actual procedure costs, using UK patient level data.	Thank you for your comment. After further discussion, the committee agreed to use UK data for length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Swansea Bay University Health Board	Evidence Review H	009	013 - 014	We believe that there are clear flaws in the data included in the Evidence Review comparing TAVI with surgery. These flaws can be summarised as an over-reliance on the inclusion of older data which are not consistent with current clinical practice, and hence the outcomes of which are not consistent with current outcomes from TAVI in the NHS. Specifically:- 1. The STACCATO trial should not be included. This trial included 100% Trans-apical access for TAVI. Outcomes from trans-apical TAVI are worse in all trials, which is why it is not used in current practice, with our unit having stopped its use in 2018. 2. The data on Trans-apical TAVI from the PARTNER 1A & PARTNER 2 trials should not be included. In these trials 29.9% and 23.9% of TAVI procedures respectively were trans-apical. The Evidence review should focus on the data from trans-femoral TAVI, which is the dominant access route in contemporary practice (100% of TAVI procedures in our unit in 2020). 3. The data on Trans-aortic / Direct aortic TAVI in the Corevalve High-risk (17.1% Trans-aortic) and SURTAVI (4.1% Trans-aortic) trials should be excluded. Like Trans-apical access, Trans-aortic access is associated with worse outcomes, and is no longer used in contemporary practice (<0.5% UK TAVI Registry 2019-20) 4. The Evidence review should have analysed the trans-femoral TAVI data separately, as has been done within all of the included trials, and within multiple previous meta-analyses. A comparison of trans-femoral TAVI and surgical AVR would be far more relevant to current practice. This	Thank you for your comment. The committee has considered these points as follows: 1. The STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has been excluded from the economic modelling based on the transapical access route not being in line with current practice. 2. The committee agrees that the proportion of transapical procedures are higher than in current UK practice. However, the committee does not believe that across the UK the proportion of patients having transapical TAVI is 0% and so in line with the review protocol, the PARTNER trial data have been included as a combined

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				was the approach taken in the ESC/EACTS and in the ACC/AHA guidelines. 5. The Review should give greater weighting to more contemporary trials which are more reflective of current practice and outcomes. The PARTNER 1A trial began recruiting in 2007, and the CoreValve High Risk trial in 2010. Both PARTNER 2A and SURTAVI are also older trials which do not reflect current clinical practice and are specific examples of how the older trials bear no resemblance to current clinical practice, whereas the more contemporary trials (PARTNER 3 and Evolut Low Risk) are much closer to current practice, evidenced by the latest data from the UK TAVI Registry 2019-20 (www.bcis.org.uk) a. TAVI Valve type. All of the above trials used valve technology that is obsolete. These older valves were associated with far higher rates of valve-related complications, specifically paravalvular aortic regurgitation, but also pacemaker implantation, valve embolization, need for re-intervention etc. b. Access route. Trans-femoral access is associated with superior outcomes. Rate of trans-femoral access in the trials included compared to UK TAVI registry data was as follows: PARTNER 1A 70.1%, Corevalve High Risk 82.8%, PARTNER 2 76.7%, SURTAVI 93.6%, NOTION 96.5%, PARTNER 3 100%, Evolut Low Risk 99.0%, UK TAVI Registry 96.9%, our unit 100%. c. General anaesthesia. GA means a longer procedure, slower recovery, longer hospital stay, and greater use of resources. In our unit only 1.4% of patients undergoing TAVI have required general anaesthesia in the last 3 years.	data for transfemoral and transapical TAVI. 3. Similarly, the CoreValve high risk and SURTAVI trial data cannot be excluded from the analysis post-hoc. Additionally, it would be inappropriate to exclude the CoreValve study as it is one of only few trials in the high risk cohort. 4. TAVI route of access was included as a subgroup analysis to explore if heterogeneity was found, and not as a stratification factor in the clinical review. There were not large differences in effect estimate between the overall analysis and the transfemoral subgroup analysis. As the recommendation was driven by the cost effectiveness evidence no changes have been made to the clinical review regarding the route of access as this would not affect

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				6. The Evidence Review should have included data from the UK TAVI trial, which have been presented at the American College of Cardiology in 2020. These data are 100% UK-based, and more contemporary than most of the included trials. 7. The Evolut Low risk trial data have been included sparingly.	the conclusions of the committee. In the revised version of the health economic model, only recent trials on 2nd and 3rd generations valves were used to estimate relative treatment effects. Those are prevalently on transfemoral approach. 5. It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. In the revised version of the health economic analysis only recent trials on new generation valves are included, so a weighting was not necessary. A . The committee acknowledge that the older valve types are associated with higher rates of valve complications. However,

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					only 3 studies used 2nd or 3rd generation devices. Only the outcomes of these studies were used in the health economic model to better represent contemporary practice. b. The meta-analysis used for the model is predominantly on trials with transfemoral access. c.The committee acknowledge that general anaesthesia is required much less often for TAVI in current practice than historically. However, as above, it was not considered to be appropriate to exclude older trials from the main analysis in the clinical review. 6.The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					limited to 1 year follow at present, and we have sufficient published data with longer-term follow-up. However, hospital LOS and ICU from UK TAVI trial were used to inform the model. 7.The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. The reason for being separated initially was because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Evidence Review H	051	Table 5	In the Clinical Evidence Summary (Table 5), the Evidence review has not included the data from Evolut Low risk, even though they are published and available and, as outlined above, are far more contemporary and more representative of current TAVI practice and outcomes than most of the data that are included	Thank you for your comment. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. It had previously been analysed separately because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Evidence Review H	133	005 - 009	The use of older data including some inappropriate data, and the exclusion of some more contemporary data, means that the relative outcomes of TAVI compared to surgery stated in the Evidence Review are not reflective of contemporary data. Specifically:- a. The Evidence Review states that there is a signal of harm for mortality for TAVI at 12 months. However, all of the 3 most recent trials (PARTNER 3, Evolut Low Risk, UK TAVI) showed lower 12-month mortality with TAVI than surgery. Published meta-analyses have also consistently shown lower 12-month mortality with TAVI. The Evidence review includes some previous meta-analyses, but has excluded published meta-analyses of the trials of TAVI vs SAVR for Low surgical risk patients. These published meta-analyses all show superior 1-year outcomes for TAVI. Furthermore, the Committee's own meta-analysis in the Economic model shows a very strong trend for reduced 12-month mortality, even though it has excluded data from Evolut Low-risk and UK-TAVI, both of which were associated with numerically reduced 12-month mortality for TAVI vs SAVR. b. The Evidence Review states that there is a signal of harm for TAVI with re-hospitalisation. Both PARTNER 3 and Evolut Low Risk showed	Thank you for your comment. Evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes) and is not restricted to 12 months. Published meta-analyses that were excluded were used to identify studies relevant to this review and all relevant studies in the low-risk population were included in evidence review H. The health economics analysis took a different approach as we were interested to capture short-term mortality benefits to assess cost-effectiveness. Hence, we looked at mortality benefits at 1 and 2 years and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				significantly reduced hospitalisation at 12 months for TAVI. The Evidence review has not included the Evolut Low risk data. The Evolut Low risk trial publication includes the incidence of re-hospitalisation for heart failure at 12 months, which is 6.5% for surgery vs 3.2% for TAVI.	assumed no benefit in the long-term, as found in the clinical review. We note also that the risk ratios or hazard ratios did not suggest large differences between the two groups for these outcomes but the committee considered any difference in mortality based on the absolute risk difference to be important. This is described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for most outcomes and the role health economic modelling had in the decision process. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Evidence Review H	133	014	The Evidence Review concludes that TAVI is associated with a significantly higher rate of re-intervention than surgery. However, the data this is based on are flawed. Firstly, the data come from 1 trial only (PARTNER 2). Secondly, the TAVI valve used in this trial (SAPIEN XT) is no longer available, having been superseded in 2016 by a newer iteration (SAPIEN 3 / SAPIEN 3 Ultra), which has far better procedural outcomes, particularly with respect to paravalvular leak (PVL) / aortic regurgitation, but also to structural valve degeneration (SVD). Thirdly, re-intervention after TAVI is	Thank you for your comment. Data on the need for re-intervention outcome was available from 6 further trials in addition to PARTNER 2, but these were analysed separately because only PARTNER2 reported this as a time-to-event outcome. All data were

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				driven primarily by PVL. Since PVL is much less with contemporary valves, re-intervention is also much less. In the UK TAVI trial, the rate of re-intervention at 12 months was 2.2% for TAVI versus 2.9% for SAVR. Data from our unit show a 1.4% re-intervention rate at 12 months in 2019 and a 0% rate in 2020.	considered when the committee discussed the evidence. In the revised version of the model, reintervention risk ratio is calculated using studies on 2nd and 3rd generation valves. A scenario analysis where this figure is calculated from the Evolut and PARTNER 3 only was conducted as well. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. The point about need for re-intervention possibly reducing with more contemporary valves was discussed with the committee and incorporated into the discussion section of the evidence review

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Swansea Bay University Health Board	Guideline	012	003 - 005	We completely disagree with the draft recommendation that all patients with severe aortic stenosis should be offered surgery as "first-line treatment", with TAVI considered only for patients who are "unsuitable" for surgery with non-bicuspid anatomy. This recommendation is at odds with current guidance from other societies and organisations around the world. It appears to have arisen from a misunderstanding of the current clinical context of the treatment of severe AS by TAVI, from an evidence review that prioritises older data and omits more contemporary evidence, and from a flawed economic model from which we cannot recognise our current service delivery. The specific disagreements with the draft guidelines are listed below.	Thank you for your comment. These points have been addressed in the subsequent comment boxes below.
Swansea Bay Universit	Guideline	012	003 - 005	1. The Recommendation is in complete contradiction to international guidelines.	Thank you for your comment. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
y Health Board				The 2017 European Society of Cardiology & European Association of Cardiothoracic Surgery guidelines give TAVI a Class 1 indication for patients unsuitable for surgery, and for patients at high and intermediate surgical risk "with TAVI favoured in elderly patients suitable for trans-femoral access". These Guidelines were produced before the publication of the low-risk trials, and are due to be updated later in 2021, when they are likely to recommend TAVI in low surgical risk patients. The 2020 American College of Cardiology / American Heart Association guidelines give a Class 1 indication for TAVI, specifically recommending that trans-femoral TAVI is preferred to surgery in patients aged over 80, or younger with a life-expectancy of 10 years or less, and that in patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery is recommended based on shared decision-making. 2. The recommendations do not take any account of individual patient considerations, in particular age, life expectancy, frailty, co-morbidity, anatomical suitability for trans-femoral TAVI, and how these factors influence the best treatment options for patients. 3. The recommendation does not include appropriate reference to the role of the multi-disciplinary Heart team (MDT), and shared decision-making. The importance of the MDT is emphasised in all national and international guidance, including the British Heart Valve Society publication 'Network based care for heart valve disease' (2020), GIRFT Cardiothoracic Surgery report (2018), and ESC/EACTS 2017 & ACC/STS 2020 guidelines, as well	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. We have expanded on the definition of suitability for TAVI in the section 'terms used in this guideline' and now refer to life expectancy. Thank you for your comment. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				as the NICE TAVI IPG (2017). Heart team decision-making allows complex individual patient factors such as those outlines in point 2 above to be considered. We believe that the recommendation should be changed to refer to the importance of the MDT in deciding between TAVI and SAVR.	evidence relevant to the review protocol is included and reviewed for interpretation. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. The clinical and cost effectiveness of MDTs was not included in the scope

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Swansea Bay University Health Board	Guideline	012	003 - 005	5. The Recommendation would have an enormous and highly detrimental impact on clinical practice. If the proposed guidance were to be followed, there would be a huge fall in the numbers of patients having TAVI, and a huge increase in the numbers of patients having surgery. It would not be possible for surgery to deliver the increased demand, especially in the COVID and post-COVID era, and patients would face huge waits and many would die on the waiting list. Published registry data show that the mortality on a waiting list for surgery is about 4% per month. (Malaisrie, Ann Thorac Surg 2014). Our own unit data that informed our original business case for TAVI, also shows that older patients are more likely to have increased lengths of stay, particularly on ITU, which further impacts on unit capacity and referral to treatment time. 6. The draft guideline incorrectly assumes the impact that would occur if TAVI were to be recommended in patients suitable for surgery. Firstly, as stated above, TAVI is already frequently undertaken in patients suitable for surgery. Secondly, the guideline correctly states that 80% of surgery is in low-risk patients. However, the implication that most or many of these	Thank you for your comment. 5. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patients would have TAVI if it were recommended is wrong. Surgery is mostly undertaken in very low risk and much younger patients. Average age in the UK is 63 from SCTS published data, whereas average age for TAVI in the UK is 81 (UK TAVI Registry data). In line with international guidelines, TAVI would only be undertaken in low-risk patients over the age of 70-75 and who are suitable for low-risk trans-femoral TAVI for non-bicuspid disease. 7. The draft guideline gives no consideration to patient experience and patient preference. TAVI is performed under local anaesthetic, has a median hospital stay of 1.6 days (all comer data from my unit in 2020), and immediate recovery. Surgery is highly invasive, involving chest incision, general anaesthetic, intensive care stay (mean CITU stay in our unit in 2019-20 was 3 days, median 2 days, median total length of stay of 9 days and mean total length of stay of 12.7 days), and recovery period of 3-6 months, which is usually longer in older patients. TAVI is therefore a far preferable experience for patients. Patient preference should always be a factor in clinical decision-making and has been made even more prominent by the Montgomery v Lanarkshire Health Board [2015] case. In its guidance Decision making and consent (2020), the GMC advises that "doctors must try to find out what matters to patients so they can share relevant information about the benefits and harms of proposed options and reasonable alternatives". 8. The committee did not include any patient representation. Patients should be at the centre of guidelines and decision-making in the NHS. The	6. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. 7. The outcomes included in the clinical evidence review can be found in appendix A of evidence review H. They included length of hospital stay and quality of life. These also key components of the health economic model. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				failure to include patient representation may explain the failure to give sufficient focus to patient preference and patient experience. 9. The recommendation would be of particular harm to patients in the context of COVID. TAVI has substantial advantages over SAVR in the COVID and post-COVID era, since there is no requirement for ICU, and hospital stay is far shorter. This is reflected in the much greater fall in the numbers of SAVR cases done in 2020 than the fall seen for TAVI. This fall also means that the backlog of patients requiring treatment for severe AS is substantial. Between March and October 2020 in the UK there were 3196 fewer SAVRs than expected, and 1431 fewer TAVIs. (Martin et al. Circ Intervent. In press) If the proposed guidelines were to be implemented, the massive reduction in TAVI numbers and required increase in SAVR numbers would be impossible to deliver. Even if it were theoretically possible to do this, the increase in ICU usage would have hugely negative implications in hospitals where ICU capacity is under enormous pressure. In contrast, TAVI allows patients to be treated quickly, with short hospital stays, and no use of ICU.	discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. 8.There are two lay representatives on the committee who had equal status with all other committee members. We have highlighted the importance of shared decision making, where relevant, but have

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					recommended the most clinically and cost effective interventions 9. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Swansea Bay University Health Board	Guideline	012	006 - 007	The draft guideline allows no recommendation for TAVI in patients with bicuspid anatomy who are unsuitable for surgery. This is inappropriate. Although randomised trials did not include bicuspid disease, there is a substantial body of evidence from registries evaluating TAVI in bicuspid disease. For example, Forrest (2020) reported outcomes of tricuspid versus bicuspid disease treated by TAVI in the TCT registry, and showed no difference in mortality or stroke at 30 days or 12 months. TAVI in bicuspid anatomy is in routine use in the NHS. Medical therapy for AS is associated with very poor survival.	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				TAVI should be recommended in preference to medical therapy for bicuspid disease.	currently, meaning evidence should not be extrapolated.
Swansea Bay University Health Board	Guideline	012 038	003 – 005 016	4. The Recommendation is inconsistent with current clinical practice. TAVI is currently in current use across the NHS in patients who are suitable for surgery, and who may be categorised as high risk, intermediate risk, and even low risk, but in whom assessment of the individual patient by the MDT, based on age, life-expectancy, co-morbidities, and anatomy, leads to a recommendation of TAVI. For example, across the NHS TAVI would be considered "first-line therapy" for the following groups: Patients aged 80 or over, patients with frailty, patients with cognitive impairment, patients who have undergone previous cardiac surgery, patients with liver disease, patients with severe kidney disease etc. In contrast to this reality, the draft consultation states that "The committee agreed that TAVI is usually reserved for when surgery is "not suitable". The guidelines therefore reflect current clinical practice". This is totally inaccurate. For at least 10 years TAVI has been used widely in patients who would have been considered operable, but high risk. For at least 5 years TAVI has been used in intermediate risk patients, and more recently also for low risk patients, IF the patient is aged at least 75 or older, and IF the patient is anatomically suitable for low-risk non-bicuspid trans-femoral TAVI. This change has been driven by trial evidence, by heart team decision-making, and by patient preference. This reality is reflected in the increase in TAVI numbers from 2007 to the present day. BCIS data show a 20-30% annual increase in TAVI procedure numbers, from 66 in 2007, to 781 in 2010, 2516 in 2015, and 6076 in 2019-20, despite NO change in the	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				mean patient age. TAVI has increased through appropriate heart team guided recommendation of TAVI in low and intermediate risk older patients. In the document there is no mention of the criteria that make surgery "unsuitable", whilst on page 17 lines 13-17 there are recommendations on the suitability for TAVI.	possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
University Hospital Southampton NHS Foundation Trust	Comments form	Q1		**1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** The restriction of TAVI only for patients who are "unsuitable" for surgical AVR is going to require cardiac surgeons in the UK to offer far more intermediate and higher risk patients surgery than they currently do. There will also be a considerable challenge managing the expectations of many patients who are aware of TAVI and have a preference for a less invasive procedure than surgical AVR, who are now going to have to be informed that they cannot have TAVI and that surgical AVR is their only treatment option of they are suitable for surgery	Thank you for your comment. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospital	Comments form	Q4		**5. The recommendations in this guideline were largely developed before the coronavirus pandemic. Please tell us if there are any**	Thank you for your comment. NHS services are adapting to implement interventions as appropriate following

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Southampton NHS Foundation Trust				**particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication** COVID-19 has had an enormous impact on the ability of UK cardiac surgical centres to deliver cardiac surgery over the past year, and considerable waiting lists have arisen. Because TAVI can now be delivered without intensive care stays, most if not all UK TAVI centres have been able to continue to do TAVI procedures during the pandemic, and have been able to offer life-saving treatment to people with severe AS who could not have surgery for logistical reasons (e.g. lack of ITU capacity due to COVID surge patients), so similar waiting lists have not built up. However, if TAVI is now significantly restricted to NHS patients in England as a result of this guideline, it is inevitable that people with AS will die while waiting on cardiac surgical waiting lists.	national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account. We have changed the recommendations on TAVI and it is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4). We revised the economic model based on stakeholder comments but TAVI was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	010 025	No line numbers provided 016 - 017	Dialysis post TAVI or SAVR is not necessarily a permanent state. Most patients who require renal replacement therapy (RRT, including both dialysis and haemofiltration) following cardiac surgery or cardiac interventions (including TAVI) only require temporary renal support, as renal function often recovers after the insult at the time of surgery or intervention. Has this been factored into the model, or has it been assumed that if a patient requires RRT at any point after intervention that this is a permanent health state?	Thank you for your comment. Unfortunately, we lacked data to estimate how long dialysis will be needed in patients who started RRT. Different time horizons were tested in the model as scenario analyses so that the impact on the results of assuming shorter duration of interventions could be understood. The majority die in 1 year, and many in 30 days, therefore the mean duration of dialysis is not that long. This has been corrected in the revised version of the model, hence, duration and costs are much lower than it was in the consultation. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	013 - 017	Table 2	Many of the costs/inputs in Table 2 are likely to be considerably more accurate if based on contemporary UK practice rather than historical non-UK practice reported in the clinical trials quoted. These data should be available from the national cardiac audits for both cardiac surgery and TAVI hosted by NICOR on behalf of HQIP. Paravalvar leak rates with TAVI should be taken from Mack 2019 and Popma 2019 as these use the latest iterations of TAVI valves (Sapien 3 and Evolut) which are now in routine clinical use and have documented lower rates of PVL than earlier iterations of TAVI valves used in earlier RCTs. The LOS inputs for TAVI in particular do not reflect contemporary practice. Virtually no TAVI patients in the UK require an ITU stay in current practice, and patients with an uncomplicated course (of any risk level) are routinely discharged on post-procedure day 2 at the latest, with many UK centres discharging patients on the day after their TAVI.	Thank you for your comment. Outcome baseline risks now use the latest NICOR UK TAVI registry data to reflect contemporary UK practice. Likewise, PVL rates are now estimated from 2 studies on Sapien 3 valves and are in line with BCIS NICOR data. The committee decided to use UK data coming from the UK TAVI trial to inform hospital LOS and ICU in the model. These values are now expected to reflect real-world UK practice for people at low surgical risk.
University Hospital Southa	Economic report TAVI	027	Table 12	The LOS for TAVI in particular quoted in Table 12 do not reflect contemporary practice. Almost no TAVI patients require an ITU stay in current practice, and patients with an uncomplicated course (of any risk level) are routinely discharged on post-procedure day 2 at the latest, with	Thank you for your comment. After further discussion, the committee agreed to use UK data for

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
mpton NHS Foundation Trust				many UK centres discharging patients on the day after their TAVI. The recently released 2019-20 UK TAVI registry can provide accurate LOS data, but for reference, the median length of stay on approximately 140 transfemoral TAVIs in our centre in 2020-1 was 2 days.	length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial (http://www.clinicaltrialresults.org/Slides/ACC%202020/UKTAVI_Toff.pdf) as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	033	Table 21	Surely a proportion of the costs included in this Table relate to hospital stay incurred by the patient requiring a pacemaker, whereas TAVI and SAVR patients are already in hospital, and there is therefore a risk that some costs associated with pacemaker are being double counted? TAVI patients in particular are unlikely to have their hospital stay extended by requiring a pacemaker as the need for pacemaker after TAVI is usually identified within the first 24 hours and will be done immediately. SAVR patients often have to wait several days to have a pacemaker implanted due to concerns about infection in the early post-operative period	Thank you for your comment. The committee decided to now assume that all AE costs are included in the Reference Cost to avoid potential double counting. There is a sensitivity analysis where each AE is costed as a separate episode. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	039	012 - 020	Given the high likelihood that length of stay costs (both general and ICU stay) are highly likely to be overestimated for TAVI in particular, a sensitivity analysis evaluating this would also be very helpful, although re-running the whole model with more accurate inputs as per point 15 above would be even more helpful.	Thank you for your comment. After further discussion, the committee agreed to use UK data for Length of hospital stay and ICU stay as it appears clear that practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial (http://www.clinicaltrialresults.org/Slides/ACC%202020/UKTAVI_Toff.pdf) as this reflects the current practice in the NHS, and these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	040	007 - 018	Surely the impact of PVL on mortality is already captured in the RCTs that have been included in the review, and its use as a separate marker of mortality in the health economic model is therefore overestimating its costs?	Thank you for your comment. You are correct that the impact of PVL on mortality is already captured in the trial outcomes. The model is not overestimating mortality as the calibration factor approach ensures that the mortality predicted by the model is exactly the one observed from the evidence. However, the mortality beyond the trial follow-up will also be influenced

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					by PVL and this is captured in the model.
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	043	Table 31	Why are TAVI echo costs 3 and a half times higher than SAVR? Both procedures will in general require 1 echo post procedure during the hospital stay.	Thank you for your comment. The committee noted that echo is often required when the patients have paravalvular leaks which, as found in the evidence, occur more often after TAVI than SAVR. Hence, the higher cost of echo in the TAVI arm. However, in the revised model lower rates of PVL are now used. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University Hospital Southampton NHS Foundation Trust	Economic report TAVI	047	003 - 005	The improved durability of biological surgical aortic valves is by no means a given. The Trifecta surgical valve which was widely used in the UK over the last 10-15 years is now being shown to have a high failure rate	Thank you for your comment. The sentence is tentative because we do not have long-term data on the durability of more recent valves. However, we note that some stakeholders have suggested that there has been improvement over time so we think it is appropriate to keep that as a potential limitation of the analysis.
University Hospital Southampton NHS Foundation Trust	Evidence Review H	007	031	Please provide a reference for the assertion that transcatheter valves "tend to degenerate faster than the surgical valves" in the context of treatment of failing biological valve prostheses. We are not aware of any data to support this assertion and our interpretation of the randomised Partner A and B, Partner 2, US pivotal and NOTION trials is that there is no evidence of statistically significant premature valve deterioration. Indeed, there is data to support the contrary position – i.e. surgical valves have deteriorated more quickly than TAVI (NOTION – 6 year data). In addition, there is NO evidence on the long term results of sutureless surgical valves, and these should be specifically excluded from any recommendations.	Thank you for your comment. We edited this sentence to make it clear that there is no evidence of durability beyond 6-7 yrs.
University Hospital Southampton	Evidence Review H	009	General	It is disappointing that stroke at ≥12 months was not included as a primary or secondary outcome measure given differential rates between TAVI and SAVR in a number of randomised trials at 30 days and 1 year	Thank you for your comment. The committee had to prioritise the most important outcomes for decision making and agreed that intervention-

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Foundation Trust					related stroke at 30 days was the most relevant time point.
University Hospital Southampton NHS Foundation Trust	Evidence Review H	117	Table 28	In the "Uncertainty" column it is unclear how a self expandable valve result is generated from using the Partner 3 data as this trial only included balloon expandable TAVI valves. Similarly when using EVOLUT data how was a result for balloon expandable valves generated from a trial which only included self expandable valves?	Thank you for your comment. The data refer to event rates in the SAVR arm, which both trials had. So only TAVI event rates change according to the type of TAVI considered. The table column was edited to make this clearer.
University Hospital Southampton NHS Foundation Trust	Evidence Review H	129	010 - 013	The lack of clinical evidence statements is frankly inadequate. If the GC were not provided with written summaries of the enormous amount of clinical evidence included in all these Tables, it must surely have increased the likelihood that they have not fully reviewed and digested all the information they needed to reach fully informed recommendations. If the GC were provided with written clinical evidence statements (as is usual NICE practice), then they should also have been provided for the consultation.	Thank you for your comment. It is no longer NICE practice to present written clinical evidence statements as a duplication of the evidence presented in GRADE tables. However, the evidence was reviewed multiple times with the committee and discussed in detail.
University Hospital Southampton NHS	Evidence Review H	131	001 - 003	Please provide additional explanation for the statement "the costs associated with renal failure were considered to be higher and more important to capture than those of myocardial infarction". While the long-term costs of ongoing renal replacement therapy (RRT) for end-stage renal failure are clearly considerable, the number of people who require permanent RRT after surgical or transcatheter valve intervention is small, whereas myocardial infarctions in patients with heart disease are common	Thank you for your comment. We have clarified this point with the committee and reworded the explanation to ensure the reasoning is clear. Renal failure directly related to the TAVI procedure was considered to

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation Trust				and clearly associated with acute and long-term clinical and economic consequences for affected people.	be more common than myocardial infarction directly related to the TAVI procedure, which is why it was thought to be more important to capture renal failure costs. The costs associated with myocardial infarction are also included in the model.
University Hospital Southampton NHS Foundation Trust	Evidence Review H	132	034 - 037	Whilst factually correct, the importance of longer term follow up will be more important for younger patients. TAVI in the UK is still predominantly performed in people older than 80, many of whom are declined for surgical AVR, so the current lack of very long term data may not be relevant in an older population.	Thank you for your comment. We have added your point to the committee's discussion of the evidence in evidence review H.
University Hospital Southampton NHS Foundation Trust	Evidence Review H	146 - 147	General	The GC's acknowledgement of the importance of shared decision making and review by a multi-disciplinary heart team in contemporary practice is to be welcomed, however, for neither to be felt worthy of mention in the recommendations is disappointing. Especially as recommendations 1.5.3 and 1.5.4 as they currently stand will cause considerable difficulties for clinicians and distress for patients who may have a strong preference for TAVI over surgical AVR in a shared decision making approach. There is already widespread knowledge amongst people with aortic stenosis of the existence of TAVI as a treatment option, so for it not to be even considered as a possible treatment in operable patients, solely on the basis of the	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				novel health economic model conducted for this review (page 145 lines 26-9) is going to be very challenging for both patients to accept and clinicians to manage	MDTs as an example of how this may be provided.
University Hospital Southampton NHS Foundation Trust	Evidence Review H	General	General	I cannot see anywhere whether minimal important differences were defined for the outcomes reported, or was the standard difference of risk ratio of 0.8-1.25 used for all outcomes? If so, this is different to other recent NICE guidelines e.g. NG185 on acute coronary syndromes, in which the GC differentiated the clinical importance of certain key clinical outcomes such as mortality, stroke and heart attack whereby it considered smaller absolute differences in these outcome rates between interventions to be clinically relevant to patients	Thank you for your comment. In line with other NICE guidelines, the committee considered the clinical importance of outcomes based on the absolute risk difference. This is described in the methods chapter, section 2.7. The thresholds were different in this guideline to the one on acute coronary syndrome. The thresholds were based on a discussion with the guideline committee.
University Hospital Southampton NHS Foundation Trust	Guideline	006	003 - 004	Please clarify whether "documented ventricular arrhythmia" includes people with isolated ventricular ectopic beats	Thank you for your comment. We have removed documented ventricular arrythmia from recommendation 1.1.7. The committee intended to exclude ventricular ectopic beats by using this phrase, limiting the recommendation to only patients with ventricular tachycardia. However, the committee agreed that any patient with ventricular tachycardia would require assessment by a cardiologist, irrespective of the presence of mitral

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					valve prolapse, so the indication was the arrhythmia, and not the mitral valve prolapse, which is why the committee felt that this part of the recommendation was best removed.
University Hospital Southampton NHS Foundation Trust	Guideline	009	001 - 003	This recommendation (1.3.5) is vague, and gives no indication as to how "the degree and distribution of calcium in the aortic valve" should influence TAVI treatment. If the intention is (for example) to direct clinicians to offering self-expanding TAVI valves for certain patterns of valve and left ventricular outflow tract calcification, then please say so	Thank you for your comment. This detail is included within the rationale and discussion sections, for example that a very high calcium score or calcium in the left ventricular outflow tract may increase the risk associated with TAVI. We are not advocating for self-expandable valves for certain patterns of valve and left ventricular outflow tract calcification as the decision will take into account other factors such as age and suitability for surgery.
University Hospital Southampton NHS Foundation Trust	Guideline	009	004 - 005	This recommendation (1.3.6) seems unnecessarily specific and niche in the overall context of the Guideline, as MRI is not routinely performed in the assessment of people with aortic stenosis, unless the implication is that it should be offered more frequently. If that is the case, then a separate recommendation as to the utility and indication for MRI scanning in people with aortic stenosis is required	Thank you for your comment. The scope for this guideline included indications for interventions the review question for this scope topic included MRI. People have MRI for variable reasons and we are just advising on how to use the result if MRI was performed and it shows mid-

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					myocardial fibrosis. This has been clarified in the committee's discussion section.
University Hospital Southampton NHS Foundation Trust	Guideline	012	003 - 007	Given that Evidence Review H shows that minimally invasive surgical AVR is both clinically inferior and more costly than surgery via median sternotomy (see Evidence Review H, page 134 lines 33-50, and page 145 lines 31-34), how can minimally invasive surgical AVR be "offered" in preference to TAVI? The logical conclusion of Evidence Review H as it currently stands is that minimally invasive surgical AVR should NOT be offered under any circumstances, in which case recommendation 1.5.2 also needs to be amended to dealing with mitral valve surgery only. Furthermore, it is hard to reconcile the extremely strong recommendation of OFFER surgical AVR with evidence review H which shows broadly similar mortality, stroke and QOL clinical outcomes with TAVI and SAVR, and considerable uncertainty in both the published and novel cost effectiveness analyses presented, particularly given concerns about the validity of the novel cost utility model developed for the guideline, on which the whole offer only surgical AVR in rec 1.5.3 appears to rest. Although the Cost Utility Analysis for TAVI concludes on page 48 that, *"This economic evaluation demonstrated that TAVI compared to SAVR for treating aortic stenosis in patients at intermediate and high operative risk is not cost effective in England at the current price of the valve. The results of the analysis are robust to the assumptions of the model as, even in the most favourable scenario, TAVI failed to show an incremental cost effectiveness ratio below the threshold of £30,000 per*	We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. We have expanded on the definition on 'suitability for TAVI' in the section 'terms used in this guideline'. Although prices were not mentioned in the recommendations, the model includes a clear threshold analysis showing the price threshold that makes TAVI cost effective for each

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				QALY gained", this is contradicted on page 45, lines 5-11 where it states that*, "The results showed that for intermediate-risk patients, TAVI becomes cost effective at a threshold of £30,000 per QALY gained when the price drops below £10,200. For high-risk patients TAVI becomes cost effective when the price of the valve ranges between £11,000 and £12,400. This is equal to a discount of around 39%-45%. This price is not too distant from the price TAVI is currently purchased in other developed countries as France or Germany, hence, if the price in the UK drops to similar levels, TAVI may become cost effective in England at least for high-risk patients"*. There is precedent in NICE guidance for relative costs of medical devices to be included in recommendations (NICE TA 152: drug-eluting stents). Given that the cost utility analysis is highly sensitive to the current UK cost of TAVI valves, is there not an argument for the GC to make a recommendation that specifies the price threshold at which TAVI would be considered a cost effective treatment option? It is eminently possible that companies that manufacture TAVI valves will amend their valve costs in response to any number of commercial pressures in a much shorter timeframe than NICE will review and update this Guideline, which will continue to restrict TAVI in England until such time as it is ever updated. One of the key drivers of expansion of TAVI in the UK to date, has been increased referrals for TAVI from cardiac surgeons for patients who they believe to be at intermediate or high surgical risk. Very few patients are truly inoperable (on the grounds of futility or prohibitive operative risk), and the use of the term "unsuitable" in recommendation 1.5.4 is unhelpfuly vague and open to wide interpretation. Is this supposed to mean inoperable, or does it mean patients for whom the perceived balance of	risk category (between £14,000 and £15,000 in the revised version of the model).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				risks and benefits (perhaps after a shared decision making process) is in favour of TAVI? If that is the case, then an appropriate recommendation to encompass this approach should be drafted.	
University Hospital Southampton NHS Foundation Trust	Guideline	012	006 - 007	What treatment should people with bicuspid aortic valves and severe valvular heart disease be offered if they are unsuitable for surgery? The implication of rec 1.5.4 is that they should NOT be offered TAVI, but if the GC feels this is the case, it should be explicitly stated and covered by its own recommendation	Thank you for your comment. The committee has not made a 'do not' recommendation for TAVI in people with bicuspid aortic valve disease. People unsuitable for surgery would be considered for TAVI depending on individual factors.
University Hospitals Coventry & Warwickshire NHS Trust	Economic report TAVI	General		We believe that the economic modelling and assumptions within are not representative of contemporary practice at our institution. In calendar years 2019-20: • 96% of patients at our institution undergo TAVI procedures under local anaesthetic and none of these patients had a stay in intensive care. Our routine practice is for all these patients to be returned to a monitored coronary care unit or cardiac ward bed. • The median length of stay at our institution is 2 days (including day of procedure). • Post-discharge valve re-intervention rate at our hospital is 1 in 233 patients since commencing the service in 2014. That patient had TAVI for deterioration of a surgical valve (likely due to patient-prosthesis mismatch) and required balloon valvuloplasty to fracture the original surgical sewing ring and allow full expansion of the TAVI prosthesis.	Thank you for your comment. Length of hospital stay and ICU stay were changed to reflect the findings of the UK TAVI trial: 0 ICU and 3 LOS after TAVI in low-risk patients. Our estimation of cost for TAVI (without the valve) is £5,500 (3 days median LOS) which includes all the adverse event costs such as pacemaker implantation. It is not too far from the figure reported from your institution and should reflect the average cost in the NHS as it was calculated using NHS-only sources

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The service level costs for TAVI at our hospital is approximately £3850 per procedure (not including valve prosthesis costs). This includes all staffing costs, CT and echo imaging costs, bed day costs. It is based on a median 2 day length of stay at our institution.	(UK TAVI trial, NHS Reference Costs). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	012	003 - 005	We are concerned that the assumptions that the draft recommendations are based on are not reflective of contemporary practice. All TAVI data at our institution are submitted to the NICOR national database. A review of this data at our institution (presented and ratified at internal clinical governance meeting in March 2020) demonstrated the following over the calendar years 2019-2020: • Total number of procedures: 125 • Mean age of patients: 81	Thank you for your comment. The model was revised and the assumptions now compare well the information given by your institution: Intermediate risk: Post-procedural mortality: 1.9% Stroke: 2.1%

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Proportion of TAVI cases utilising local anaesthetic: 96% • Transfemoral approach: 96% • Post-procedural mortality:1.6% • Post-procedural stroke: 2.4% • Major vascular complications: 1.6% • New permanent pacemaker implantation: 9.4% • **Median length of stay: 2 days (including day of procedure)**	Vascular complications: 2.3% New permanent pacemaker implantation: 9.7% Median length of stay: 3 days TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	012	003 - 005	We disagree strongly with the draft recommendation that all patients with severe aortic stenosis should be offered surgery as first-line treatment, with TAVI considered only for patients who are unsuitable for surgery with non-bicuspid anatomy. This recommendation is not in line with contemporary heart valve disease guidelines or practice, or decisions regarding appropriate treatment at our Heart Valve multidisciplinary team meeting (MDT). It would also not be consistent with the preferences of many of our patients that are referred for heart valve intervention.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation.
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	012	003 - 005	At our heart valve MDT, we assess age, surgical co-morbidities and risk, frailty, anatomical suitability for surgical and transcatheter intervention. We also consider patient preference, which in the vast majority of cases is for TAVI where possible, as patients prefer a less invasive procedure, a shorter hospital stay, and a more rapid recovery to functional activity. In our experience, and from their feedback, this is as important to patients as long-term prognosis. Before the availability of longer-term (>5 year) follow-up data, we counselled patients that the durability of TAVI prostheses is uncertain, and yet most still preferred to have a TAVI procedure. We believe that discussions of individual patient circumstances, data, technical considerations and patient preferences at a Heart Valve MDT is	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the most appropriate way to decide on whether a patient should have surgical or transcatheter heart valve treatment. We also believe that shared decision-making with patients is paramount.	Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. The committee agree that shared decision making is central to decisions regarding intervention and this has been highlighted in recommendation 1.5.1.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	012	003 - 005	These recommendations would be challenging in practice as patients often ask for a TAVI procedure in preference to open-heart surgery. It would be very difficult to refuse a patient the option of TAVI based on the Montgomery legal ruling, suggesting that all available options for treatment should explained to a patient with attendant risks and benefits.	Thank you for your comment. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population. Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention. Recommendations for interventions could not be made for

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	012	003 - 005	Our concern is that if TAVI is only offered if surgery is not suitable, then patients will decline any intervention – leading to poorer quality of life, impaired prognosis, higher rates of hospital admissions with decompensated heart failure, and higher system-wide costs.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention. Recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	012	003 - 005	We are concerned that if the recommendations are followed, then it would be difficult at our hospital to accommodate the increased surgical procedure numbers due to the restricted availability of intensive care unit beds, longer post-operative stay and theatre availability. As a consequence, waiting times for operations would increase dramatically resulting in increased mortality, morbidity, and poorer quality of life for patients.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE guidelines focus on recommending interventions based on the best available clinical and cost-effectiveness evidence. NICE and NHSEI have published a joint implementation strategy alongside the guideline.
University Hospitals Coventry & Warwickshire NHS Trust	Guideline	General	General	The TAVI team at University Hospital Coventry & Warwickshire comprises of Dr Thirumaran Rajathurai, Dr Luke Tapp, Dr Nishant Gangil (Consultant Cardiologists and heart valve disease specialists), Sister Lauren Deegan (Heart Valve specialist nurse).	Thank you for your comment.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve for Life UK	Economic report TAVI		Table 31	Table 31 shows the costs for TAVI. For the reasons outlined in detail above, these costs are grossly inaccurate for TAVI	Thank you for your comment. We have revised the cost calculation of TAVI using UK NHS-based source such as the soon-to-be published UK TAVI trial (for length of stay), NHS Supply Chain and NHS Reference Costs. The new cost estimation accurately represents the cost of a TAVI procedure in the UK. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	007 009	018	The Economic model has worked on a Lifetime horizon, and has subsequently based this on a 30-year time-frame, as well as a 'shorter' 13-year time-frame.	Thank you for your comment. According to NICE Reference case, time horizon must be long enough to

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It is inappropriate to base the model on such a long-term timeframe for the following reasons:- 1. There are no RCT data comparing TAVI and surgery beyond 5 years. The economic model was therefore based on estimation of events, rather than real data. 2. The average age of a patient undergoing TAVI in the NHS is 81 years. The average life-expectancy of patients undergoing TAVI is therefore far less than 13 years, let alone 30 years. 3. Comparison of long-term event rates is inappropriate in a comparison of 2 procedures, where events occurring in the peri-procedural phase are largely dependent on the procedure, but events occurring later are largely independent of the procedures. Analysis of long-term events distant from the procedure should be confined to those events which are clearly valve-related i.e. valve haemodynamics, structural valve degeneration, valve failure, re-intervention for valve failure The model should be changed to a short time-frame to preserve accuracy e.g. 5 years.	reflect all important differences in costs or outcomes between the technologies being compared. This means that, typically, NICE analyses use time horizon exceeding the duration of the trials. The committee agreed to reduce the time-horizon in the base case scenario to 15 years. This should reflect the average life expectancy of 75 years old TAVI patients, who now populate the low surgical risk category. A period shorter than 15 years was considered inappropriate as some of the outcomes of TAVI and SAVR, e.g. reinterventions, occur late. Nevertheless, several scenario analyses were conducted showing the cost-effectiveness results using different time horizons: 5, 10, 15 and 30 years. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	012	018-020	The Economic model is based on the same data as the Evidence Review. This is inappropriate for the Economic model for the same reasons outlined above. Specifically:- 1. The data are dominated by older trials which, as described above, are not consistent with current practice, or current outcomes, from TAVI in the UK. As a result, the outcome data and associated costs are not representative of current practice. This will be described in more detail below 2. The data from the UK TAVI trial are not included, and would strengthen the model significantly by representing UK-based data, as well as more contemporary data 3. The data from the Evolut Low Risk trial are not included in the Economic model. It is not clear why 4. Readily available UK-specific data on outcomes and costs of TAVI in the UK from the UK TAVI database have not been used, although they are available in the public domain (www.bcis.org.uk)	Thank you for your comment. 1. The committee agreed that the model should be based on recent rather than historical data to account for valve efficiency and technological improvement. Therefore, in the base case scenario, treatment effects are now calculated using only trials of 2nd and 3rd generation valves: PARTNER 2, PARTNER 3 and Evolut. 2. The UK TAVI trial is still unpublished and so its effectiveness findings could not be included in the meta-analysis. Descriptive statistics

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				5. There is no weighting for more contemporary studies despite the fact that these are far more reflective of current UK practice, as outlined in detail above. 6. Data with trans-apical access should not be included in the Economic model, since trans-apical access is more expensive, has worse outcomes, and is only used in 1.3% of patients in the UK.	data from the trial were used to inform length of hospital stay and ICU days after TAVI and SAVR as those reflect UK practice. 3. The Evolut low risk trial has been added to the meta-analysis 4. TAVI outcomes baseline risks are now taken from the latest BCIS UK TAVI audit. 5. Only contemporary studies (2nd or 3rd generation valves) are now used in the base case analysis of the model and so weighting is no longer applicable 6. The trials used to inform the meta-analysis are now predominantly using the tranfemoral approach. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	014		The rate of moderate/severe PVL for TAVI used is 4.63%. This is based on data from old trials with obsolete valve types. With current generation valves the rate of moderate/severe PVL is much less. Only the following trials involved current generation valves: PARTNER 3 Mod/Sev PVL 0.8%; Evolut Low Risk 3.4%. In the UK TAVI registry 2019/20 Mod/Sev PVL rate was 2.3%	Thank you for your comment. We updated our model to use data for PVL that reflects the outcomes of new generation valves (SAPIEN 3). The new rate we use for moderate and severe PVL is 2.7%, which is very close to the percentage reported in the last BCIS audit for TAVI in 2019/20 for moderate and severe PVL (3%). We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	014		The re-intervention rate for surgery is based on a single registry study which is relatively small in size (<1000 patients), and which includes data on valves which are no longer in use and which had high rates of re-intervention, specifically the Mitroflow. This constitutes very poor evidence on which to base an important element of the economic model	Thank you for your comment. The paper from Rodriguez-Gabella was chosen to inform baseline risk of reintervention after SAVR as it was the only one with a follow-up covering most of the time horizon of the model (13 years last follow up, time horizon 15 years). Since, the rate of reintervention increases significantly over time, the length of follow-up is crucial. Using other data would have involved relying more on extrapolation. We are aware that efficiency improvements and new valves may have reduce the rate of re-intervention but looking at UK data, it does not seem that the model is over-estimating the number of reinterventions after surgery, at least in the short term. UK TAVI trial: 2.9%

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE model: 1.4%
Valve for Life UK	Economic report TAVI	015		The relative re-intervention rate for TAVI and surgery is highly flawed and has a significant effect on costs. Firstly, It is based on a paper (Ler (2020) that was excluded from the Evidence Review in this same Draft Recommendation. In Evidence Review 8, Appendix I (https://www.nice.org.uk/guidance/gid-ng10122/documents/evidence-review-8) NICE state that they excluded Ler (2020) on the grounds that 'methods are not adequate/unclear'. Secondly, the data included in Ler are from older studies using valves which are now obsolete. These valves were associated with much higher rates of moderate/severe PVL, which was the main reason for re-intervention after TAVI. Current generation valves have far lower rates of PVL, as has been described above, and hence lower rates of re-intervention. The Economic model uses the Ler paper to suggest that the Odds Ratio for re-intervention for TAVI vs Surgery is 3.52 at 1 year, 3.55 at 2-3 years, and 3.55 at 5 years. In fact, more contemporary trials, using valves that are actually in current use, are completely different. In PARTNER 3 the rates of aortic valve re-intervention at 1 year for TAVI vs surgery were 0.6% and 0.5% respectively, in Evolut Low Risk they were 0.7% and 0.6% respectively, and in UK TAVI they were 1.1% for TAVI and 1.6% for surgery. In other words, no difference in re-intervention at 1 year with current generation valves. The use of an odds ratio of 3.55 at 1 year in the Economic model is therefore clearly inappropriate. Finally, the model assumes that the relative rate of re-intervention for TAVI and SAVR will be the same over a 30-year time period. This is clearly flawed since there are no data beyond 5 years. More specifically, re-	Thank you for your comment. Ler 2020 was excluded from the clinical review for being a literature review which did not meet the review protocol criteria (see appendix A in evidence review H), though it was included as an evidence for the model. After further discussion the committee agreed to exclude this evidence as it was clearly focused on old generation valves not reflecting contemporary practice, as your comment highlighted. Relative treatment effects for reintervention now come from the trials included in the literature review as these were fully discussed and reviewed by the committee. In the base case we are now only using the treatment effect captured in trials

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intervention in the first 5 years for TAVI will be predominantly for paravalvular AR. After 5 years paravalvular AR will no longer be a cause of re-intervention. Re-intervention after 5 years for TAVI and SAVR will be mainly for structural valve degeneration, which will happen with both TAVI and SAVR, with no evidence to suggest a higher rate for TAVI. It is therefore wrong to assume that the relative rate of re-intervention after 5 years will be the same as it was in the first 5 years. Figure 6 illustrates how flawed the model's assumptions on re-intervention are, suggesting as it does that the relative rate for TAVI to SAVR will be approximately 3.5:1 annually in perpetuity.	evaluating 2nd and 3rd generation valves: • PARTNER 2 • PARTNER 3 • EVOLUT Also, we added a sensitivity analysis where this figure is instead calculated from Evolut and Partner 3 only, with a relative risk close to 1. We are aware that a major challenge of this model is the extrapolation of treatment effects beyond 5 years as trials usually have a shorter follow-up. As per NICE reference case, we now use a longer time-horizon (of 15 years) in order to capture all important differences in costs or outcomes We are aware that there might be more uncertainty around outcomes in the longer term. Therefore, scenario analyses have been conducted for several alternative time horizons (5, 10, 30 years).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	016		The data used on costs of ICU stay for TAVI are inappropriate. The Model has based costs on an average ICU stay of 2 days for intermediate risk patients, and 3 days for high-risk. These assumptions are based on data from the trials which are a. old b. reflect the US model of care for TAVI. Currently in the NHS patients do not go to ICU at all after TAVI. The average number of days on ICU for TAVI in the NHS is Zero for intermediate risk and Zero for high-risk. These data are evident from the UK TAVI trial, in which the median length of stay on ICU was 0 days for TAVI (inter-quartile range 0,0), versus median 1 day (IQR 1,3) for surgery. This has led to a major overestimation of the costs of the TAVI procedure.	Thank you for your comment. After further discussion, the committee agreed to use UK data for length of hospital stay and ICU stay as it appears clear that the practice in the UK is very different from the practice in the USA (where the majority of the trials were conducted). Length of hospital stay and ICU stay in the low-risk population now come from the UK TAVI trial as this reflects the current practice in the NHS, and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					these numbers were used to extrapolate ICU and hospital LOS in the other risk groups. For all risk groups, ICU for TAVI was set to 0 as it appears to be very unlikely for a person to need ICU after TAVI in England. The costs of a TAVI procedure for all risk groups (without the valve) were estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

<table>
<tr><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>for people at intermediate or low surgical risk (1.5.3).

NICE and NHSEI have published a joint implementation strategy alongside the guideline.</td></tr>
<tr><td>Valve for Life UK</td><td>Economic report TAVI</td><td>016</td><td></td><td>The data used for Total Length of Stay are also inappropriate. The model uses a LOS of 6 and 8 days for TAVI in intermediate and high risk respectively vs 9 and 11 days for surgery. This is very far from current practice for TAVI. Hospital stay was much lower in PARTNER 3 and Evolut Low Risk. The UK TAVI trial data show median LOS 3 days for TAVI vs 8 days for SAVR. UK TAVI registry data show median LOS 2 days for TAVI. This has further contributed to overestimation of the costs of the TAVI procedure.</td><td>Thank you for your comment.

For LOS the model now uses UK TAVI trial data for the low risk category: 3 days for TAVI and 8 for SAVR. These numbers were scaled up to find the numbers for intermediate and high risk patients using the analysis on hospital resources from Reinhoul (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619014/)

This resulted in the following values:
<table>
<tr><th>Hospital resource</th><th>Risk</th><th>TAVI</th></tr>
<tr><td rowspan="3">Hospital LOS</td><td>Low</td><td>3</td></tr>
<tr><td>Intermediate</td><td>3.2</td></tr>
<tr><td>High</td><td>3.3</td></tr>
<tr><td>ICU LOS</td><td>Low</td><td>0</td></tr>
</table>
</td></tr>
</table>

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

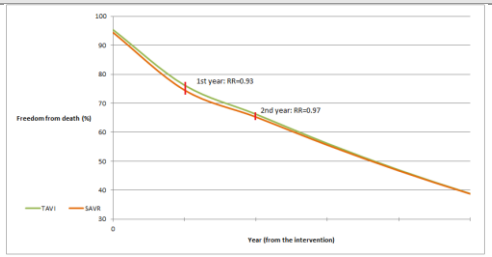
Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Intermediate 0 1.5 High 0 1.8 We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	017		The Economic Model has based procedural cost for TAVI on NHS Reference costs, £9658 for intermediate-risk and £11979 for high-risk. However, many centres are now on aligned incentive, or block contract payment models. Furthermore, all centres are expected to move away from payment by results in the next 1-2 years. It would therefore be more appropriate to base procedure costs on the actual procedure costs, using patient level costing, or PLICS, data. Analysis from Liverpool Heart & Chest Hospital of PLICS data for 244 TAVIs in a recent calendar year showed the average cost of TAVI to be £6332. For trans-femoral TAVI it was £5678. Analysis of PLICS data from Leeds Teaching Hospitals NHS Trust found an average TAVI cost of £5322 per patient. The base case	Thank you for your comment. We revised our approach to use a UK source instead of US-based trials to estimate length of hospital stay and ICU stay after TAVI and SAVR. Consequently, our estimation of costs of a TAVI procedure has changed.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				should be revised to reflect the lower true cost of TAVI, or at the very least the different potential cost of the TAVI procedure should be added to the sensitivity analyses.	The costs of a TAVI procedure for all risk groups (without the valve) are now estimated as the following: High risk: £5,479 Intermediate risk: £5,540 Low risk: £5,572 These estimates are in line with the costs provided by several NHS trusts around England. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	022		The 12-month mortality meta-analysis has not included the Evolut Low Risk trial, even though this trial has reported 12 month mortality. The 12-month mortality meta-analysis also does not include UK TAVI, which had lower 12 month mortality with TAVI versus surgery, and which data is in the public	Thank you for your comment.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				domain. The inclusion of these trials would, as in all previously published meta-analyses, demonstrated significantly lower 12-month mortality with TAVI. Even this meta-analysis shows a strong trend to reduced `12 month mortality with TAVI. However, despite this there is a statement in the Evidence review that TAVI was associated with a signal of harm for mortality	Evolut has now been added to the meta-analysis for all the treatment effects, including mortality. The UK TAVI trial could not be added as it still unpublished. The evidence review looked at long-term mortality (using the last follow-up available) and therefore found no difference in mortality. For the economic model, we conducted separately the meta-analysis on mortality at 1 and 2 years to capture the short-term benefit in mortality at 12 months that was indeed reported in several trials. Beyond this point, data available suggest no or little (0.97 at 2 years) benefit. Therefore, we modelled mortality so that it accurately reflects the short-term benefit but converge in the long-term, as the available evidence suggest (see the graph):

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					 We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	042	Table 30	Table 30 shows the events per 1000 patients in the Economic model and demonstrates the use of inappropriate data drawn from old trials that are not reflective of contemporary TAVI practice and outcomes ; In particular:- a. Stroke. The data in the model show that strokes are higher with TAVI. Contemporary studies show lower stroke rate with TAVI (PARTNER 3,	Thank you for your comment. a. The meta-analysis used in the base case analysis of the model was

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Evolut Low Risk), or no difference (UK TAVI). The model did not use data from Evolut Low Risk or UK TAVI despite their greater relevance to contemporary practice. b. Hospitalisation. The data in the model show that hospitalisations far higher with TAVI. Contemporary trials (Evolut Low Risk, PARTNER 3) show far fewer hospitalisations with TAVI. These data are much more contemporary and close to current clinical practice. c. Re-intervention. As described above, the odds ratio used for re-intervention is inappropriate. d. Major bleeding, major vascular complications, pacemaker. All would be lower if the economic model had included Evolut Low Risk and UK TAVI, had given greater weighting to more recent trials and less to older trials, and had excluded non-femoral access.	updated to include Evolut trial and limited to 2nd and 3rd generation valves only (PARTNER 2, PARTNER 3, Evolut). UK TAVI trial could not be included as it is currently still unpublished. b. Likewise, the hospitalisation meta-analysis now includes only trials of second and third generation valves. The studies suggest a higher hospitalisation with SAVR in the first year, but lower for the years beyond the first one. Therefore, the model applies 2 different transition probabilities and hazard ratios. c. Ler 2020 was excluded and reintervention relative treatment effect is now informed by the meta-analysis of the PARTNER 2, PARTNER 3 and the Evolut trial. A scenario analysis with a relative risk close to 1 was tested as well.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					d. The trials in these revised meta-analyses predominantly used transfemoral access. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Economic report TAVI	General		Valve for Life UK believes that the TAVI Economic Model represents the most flawed element of the Draft Guideline. The principal problem with the Economic model is that is constructed using data drawn from old trials of TAVI versus surgery, which are not reflective of current clinical practice, and hence costs, as well as outcomes and their associated costs, are grossly inaccurate, leading to grossly inaccurate assessment of cost-effectiveness. In addition, the costs of the TAVI procedure are significantly overestimated, and are not representative of current NHS TAVI costs.	Thank you for your comment. The model has been revised following stakeholder comments and, in its current state, it uses only treatment effects coming from 2nd and 3rd generation valves to better reflect current practice.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We will further outline more specifically the flaws in the Economic model below	Costs were also updated to reflect the UK practice and are taken from UK NHS sources only: UK TAVI trial for length of hospital stay and ICU stay, NHS Reference Costs 2018-2019 for the cost of the procedure and NHS Supply Chain for the average price of a TAVI valve. We think that the revised model is accurately reflecting the cost of a TAVI procedure in the UK. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve for Life UK	Economic report TAVI	General		The results of the Economic model are not consistent with previous cost-effectiveness analyses of TAVI. This is easily explained by the flaws in the model which we will describe in detail below	Thank you for your comment. The revised economic model presents results that are now more in line with other recent economic analyses; High risk ICER: • NICE model: £14,000 • Tarride 2019 (Canada): £9,510 (they used a cheaper price for TAVI) Intermediate risk ICER: • NICE model: £50,000 • Kodera 2018 (Japan): £51,210 • Tam 2018 (Canada): £43,055 • Goodall (2019) found that TAVI dominates SAVR but their analysis is using French prices for valves which are priced much lower than the ones in the UK. To give an example, a Sapien 3 valve in France is charged around £12,000 (source: https://www.legifrance.gouv.fr/jorf/article_jo/JORFARTI00003

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					6577833) whereas the average price of a TAVI valve in the UK is £17,500 (source: NHS Supply Chain). At this price, NICE model reaches the same conclusion as Goodall • Tarride 2019: £15,500. Though they use a cheaper price for the valve as in Canada Sapien 3 is charged less (£14,500). At the same price, the guideline model predicts TAVI to be cost-effective as well. Low risk ICER: • NICE model: £136,000 • Tam 2018: £15,900 but they used Canadian price for Sapien 3 (£14,500). At the same price the guideline model predicts TAVI to be cost-effective in low risk as well. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Evidence Review	040	003-017	Randomised trial evidence for surgical treatment of secondary (ischaemic) mitral regurgitation is limited to two relatively small studies which only examined treatment of MR in patients undergoing surgical revascularisation. A total of 551 patients were included in both studies, with no survival benefit seen in either study, and higher rates of recurrent mitral regurgitation seen in the repair vs the replacement group. However, despite these limited dagta it is considered entirely reasonable to repair or replace the mitral valve in the setting of concomitant bypass surgery. This is reflected in international guidelines, although the strength of the recommendation (IIa) is also is reflective of the relatively weak evidence base. The extrapolation of this limited data to recommend surgical treatment as first line therapy for isolated functional mitral regurgitation is completely incorrect. Surgical mitral valve repair is rarely performed as a stand-alone procedure (without revascularisation) and replacement is almost never used. Surgical treatment has never been randomised against medical	Thank you for your comment. We entirely agree and have edited the recommendations to clarify the intended meaning as being for those 'undergoing cardiac surgery for another indication' as opposed to the original wording of 'an indication for surgery'.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				therapy, and in all contemporary series mitral valve repair is associated with a significant rate of recurrent mitral regurgitation. The mainstay of therapy for functional MR remains medical therapy, particularly in patients with a reduced ejection fraction. The recommendation should emphasise the importance of optimisation of guideline-directed medical therapy, cardiac resynchronisation and involvement of the specialist heart failure team in patient management.	
Valve for Life UK	Evidence Review	042	005-017	It is unclear why data is pooled from the two large Mitraclip studies (Mitra-FR and COAPT) and the CARILLON study. The Mitraclip trials are large randomised studies, appropriately powered to detect meaningful differences in major end-points, whereas the CARILLON study examined the effect on left ventricular volumes and mitral regurgitant volumes in approximately 100 patients, using an annuloplasty device rather than leaflet repair, with no reported outcome data. The study should not be included in any combined analysis which should be restricted to Mitra-FR and COAPT. Mitraclip is associated with a mortality benefit, and reduced heart failure admissions in COAPT, but not the Mitra-FR study. The reasons for the disparity between the studies are complex, but are primarily driven by patient selection. Patients in COAPT had more severe MR, less advanced left ventricular remodelling and were on better medical therapy. The health economic analysis quoted suggests an incremental cost per QALY of £30000 for Mitraclip in the specific 'COAPT-like' population. In contrast to the comments made in the text this is within the threshold for consideration by NICE. It is even more striking that Mitraclip confers an increase in median survival of 3.8 years compared to 2.3 with guideline- directed	Thank you for your comment. In line with the published protocol for this review, there were no factors on which to stratify these studies. The committee did discuss the differences in patient selection between the Mitra-FR and COAPT studies in detail when considering the evidence. We would also like to confirm that the CARILLON trial was not used within the economic model because the population did not match the severe group that the model focused on. The health economic analysis showed that MitraClip is near the threshold of cost-effectiveness in the UK. Generally, interventions are

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				medical therapy alone in this group of patients. The trial demonstrated substantial benefits of the device over medical therapy, is cost effective, and should be recommended for use in a proportion of patients with functional MR.	recommended only when their ICER is below £30,000 or £20,000. For this reason, although the committee recommended to use medical management in preference of MitraClip in inoperable patients with functional MR, MitraClip is now recommended on those whose symptoms do not improve with medical management (1.5.14). This is a compromise that takes into account the fact that MitraClip is close to cost-effectiveness according to the economic analysis and published literature (Shore 2020).
Valve for Life UK	Evidence Review H	009 General	013 - 014	Valve for Life believes that there are clear flaws in the studies / data included in the Evidence Review comparing TAVI with surgery. These flaws can be summarised as an over-reliance on the inclusion of older data which are not consistent with current clinical practice, and hence the outcomes of which are not consistent with current outcomes from TAVI in the NHS. Specifically:- 1. The STACCATO trial should not be included. This trial included 100% Trans-apical access for TAVI. In the UK in 2019-20, Trans-apical access was used in 1.3% of TAVI cases (UK TAVI Registry	Thank you for your comment. The committee has considered these points as follows: 1,The STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol. It had very low weighting in the meta-analysis owing to the imprecise estimates. However,

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Data, www.bcis.org.uk). Outcomes from trans-apical TAVI are worse in all trials, which is precisely why it is not used in current practice. 2. The data on Trans-apical TAVI from the PARTNER 1A & PARTNER 2 trials should not be included. In these trials 29.9% and 23.9% of TAVI procedures respectively were trans-apical. The Evidence review should focus on the data from trans-femoral TAVI, which is the dominant access route in contemporary practice (96.9% of TAVI procedures in the UK in 2019-20). 3. The data on Trans-aortic / Direct aortic TAVI in the Corevalve High-risk (17.1% Trans-aortic) and SURTAVI (4.1% Trans-aortic) trials should be excluded. Like Trans-apical access, Trans-aortic access is associated with worse outcomes, and is no longer used in contemporary practice (<0.5% UK TAVI Registry 2019-20) 4. The Evidence review should have analysed the trans-femoral TAVI data separately, as has been done within all of the included trials, and within multiple previous meta-analyses. A comparison of trans-femoral TAVI and surgical AVR would be far more relevant to current practice. This was the approach taken in the ESC/EACTS and in the ACC/AHA guidelines. 5. The Review should give greater weighting to more contemporary trials which are more reflective of current practice and outcomes. The PARTNER 1A trial began recruiting in 2007, and the CoreValve	this trial has been excluded from the economic modelling based on the transapical access route not being in line with current practice. 2.The committee agrees that the proportion of transapical procedures are higher than in current UK practice. However, the committee does not believe that across the UK the proportion of patients having transapical TAVI is 0% and so in line with the review protocol, the PARTNER trial data have been included as a combined data for transfemoral and transapical TAVI. a. Similarly, the CoreValve high risk and SURTAVI trial data cannot be excluded from the analysis post-hoc. Additionally, it would be inappropriate to exclude the CoreValve study as it is one of only few trials in the high risk cohort. 3.TAVI route of access was included as a subgroup analysis to explore it heterogeneity was

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				High Risk trial in 2010. Both PARTNER 2A and SURTAVI are also older trials which do not reflect current clinical practice. The following are specific examples of how the older trials bear no resemblance to current clinical practice, whereas the more contemporary trials (PARTNER 3 and Evolut Low Risk) are much closer to current practice, evidenced by the latest data from the UK TAVI Registry 2019-20 (www.bcis.org.uk) a. TAVI Valve type. All of the above trials used valve technology that is obsolete. These older valves were associated with far higher rates of valve-related complications, specifically paravalvular aortic regurgitation, but also pacemaker implantation, valve embolization, need for re-intervention etc. b. Access route. Trans-femoral access is associated with superior outcomes. Rate of trans-femoral access in the trials included compared to UK TAVI registry data was as follows: PARTNER 1A 70.1%, Corevalve High Risk 82.8%, PARTNER 2 76.7%, SURTAVI 93.6%, NOTION 96.5%, PARTNER 3 100%, Evolut Low Risk 99.0%, UK TAVI Registry 96.9% c. General anaesthesia. GA means a longer procedure, slower recovery, longer hospital stay, and greater use of resources. Rate of GA in the trials included in which it was reported compared to UK TAVI registry data was as follows: Corevalve High Risk 94.6%, SURTAVI 75.7%, NOTION 81.7%, PARTNER 3 34.9%, Evolut Low Risk 56.9%, UK TAVI Registry 9.3%	found, and not as a stratification factor in the clinical review. There were not large differences in effect estimate between the overall analysis and the transfemoral subgroup analysis. As the recommendation was driven by the cost effectiveness evidence no changes have been made to the clinical review regarding the route of access as this would not affect the conclusions of the committee. In the revised version of the health economic model, only recent trials on 2nd and 3rd generations valves were used to estimate relative treatment effects. Those are prevalently on transfemoral approach. 4.It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. In the revised version of the health

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				6. The Evidence Review should have included data from the UK TAVI trial, which have been presented at a major international conference (American College of Cardiology 2020), and hence are in the public domain. Although not published in a peer-review journal, (currently under review) these data have huge value in being 100% UK-based, and in being more contemporary than most of the included trials. The UK TAVI Steering Group would be able to give NICE access to all necessary data if requested. The Evolut Low risk trial data have been included sparingly. Firstly, the trial has been treated separately from the other RCTs, for reasons that are unclear. Secondly, data on hospitalisation are not included, even though they have been published. Thirdly, data on 12-month mortality have not been included, even though they have been published. Fourthly, data on hospital stay have not been included, even thought they were reported in the original trial presentation.	economic analysis only recent trials on new generation valves are included, so a weighting was not necessary. b. The committee acknowledge that the older valve types are associated with higher rates of valve complications. However, only 3 studies used 2nd or 3rd generation devices. Only the outcomes of these studies were used in the health economic model to better represent contemporary practice c. The committee acknowledge that general anaesthesia is required much less often for TAVI in current practice than historically. However, as above, it was not considered to be appropriate to exclude older trials from the main analysis in the clinical review. d. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow at present, and we have sufficient published data with longer-term follow-up. e. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. The reason for being separated initially was because the invasiveness of surgery was unclear. We have checked the outcome data for this trial and can

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					confirm that hospitalisation for heart failure has been included under 'onset or exacerbation of heart failure' outcome rather than hospitalisation. The 12-month mortality data are not included as there is data for 24 months and the protocol specified that we will use longest follow-up available. Regarding hospital length of stay data, we were unable to find this reported in any peer-reviewed source and so cannot include it within the analysis. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Evidence Review H	051	Table 5	In the Clinical Evidence Summary (Table 5), the Evidence review has not included the data from Evolut Low risk, even though they are published and available and, as outlined above, are far more contemporary and more representative of current TAVI practice and outcomes than most of the data that are included	Thank you for your comment. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Evidence Review H	051 - 053	Table 5	The Evidence Review concludes that TAVI is associated with a significantly higher rate of re-intervention than surgery. However, the data this is based on are flawed. Firstly, the data come from 1 trial only (PARTNER 2). Secondly, the TAVI valve used in this trial (SAPIEN XT) is no longer available, having been superseded by a newer iteration (SAPIEN 3 / SAPIEN 3 Ultra), which has far better procedural outcomes, particularly with respect to paravalvular leak (PVL) / aortic regurgitation, but also to structural valve degeneration (SVD). Published data have shown that SAPIEN 3 has better outcomes up to 5 years compared to SAPIEN XT, with valve haemodynamics and SVD equivalent to SAVR (Pibarot 2020). Thirdly, re-intervention after TAVI is driven primarily by PVL. Since PVL is much less with contemporary valves, re-intervention is also much less. Basing the evidence for the relative risk of re-intervention on 1 study of an outdated TAVI valve is therefore completely inappropriate. In the UK TAVI trial, the rate of re-intervention at 12 months was 2.2% for TAVI versus 2.9% for SAVR. These data are UK-based, far more contemporary, and would have been much more appropriately used than the PARTNER 2 data.	Thank you for your comment. Data on the need for re-intervention outcome was available from 6 further trials in addition to PARTNER 2, but these were analysed separately because only PARTNER2 reported this as a time-to-event outcome. All data were considered when the committee discussed the evidence. The revised version of the model includes a scenario analysis where reintervention treatment effect is calculated from Evolut and PARTNER 3 only, to account for the improvement of latest generation valves whereas treatment effects in the base case scenario are calculated using a 2nd and 3rd generation valve trials. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. The point about need for re-intervention possibly reducing with more contemporary valves was discussed with the committee and incorporated into the discussion section of the evidence review. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve for Life UK	Evidence Review H	132 - 133	041 - 019	The Evidence Review summarises the relative outcomes of TAVI and surgery based on the data from the 7 trials included. Once again, the inclusion of inappropriate data has resulted in the presentation of relative outcome data for surgery and TAVI which is not representative of current outcomes from TAVI in the UK. As outlined above, if the committee had excluded STACCATO, excluded Trans-apical and Trans-aortic data, given greater weighting to the more recent and more contemporary trials, and included the UK TAVI trial, the relative outcomes of TAVI and surgery would have been more appropriate, more reflective of current outcomes, and less biased against TAVI, since TAVI procedure and outcomes have changed far more over the past 15 years than those of surgery. The data below show how key outcomes from TAVI are dramatically worse in the older trials (STACCATO, PARTNER 1A, CoreValve High-Risk, PARTNER 2, SURTAVI), and are dramatically better in the more contemporary trials (PARTNER 3, Evolut Low Risk), and closer to the UK TAVI trial and UK TAVI registry data. The Evidence Review should, as described above, give greater weighting to the more recent data, should exclude STACCATO and Trans-apical and Trans-aortic data, and should include the UK TAVI Trial data Specifically:- a. 30-day mortality: STACCATO 5.9%, PARTNER 1A 3.4%, CoreValve High-Risk 3.3%, PARTNER 2 3.9%, SURTAVI 2.2%, NOTION 2.1%, PARTNER 3 0.4%, Evolut Low Risk 0.5%, UK TAVI Trial 1.8%, UK TAVI Registry 1.3%	It was not possible to give higher weighting to the more recent trials in the analysis, as this would mean inappropriately giving higher weighting to trials in the low risk cohort because the more recent trials were in this population. In the revised version of the health economic analysis only recent trials on new generation valves are included, so a weighting was not necessary. However, although the STACCATO trial remains included in the main analysis for the clinical review, as per the prespecified review protocol, it had very low weighting in the meta-analysis owing to the imprecise estimates. However, this trial has now been excluded from the economic modelling based on the transapical access route not being in line with current practice. We have revised the economic model based on stakeholder comments and have changed the recommendations.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				b. 30-day stroke: STACCATO 8.8%, PARTNER 1A 4.6%, CoreValve High-Risk 4.9%, PARTNER 2 5.5%, SURTAVI 3.4%, NOTION 1.4%, PARTNER 3 0.6%, Evolut Low Risk 3.4%, UK TAVI Trial 2.4%, UK TAVI Registry 2.1% c. 30-day major bleeding: STACCATO 2.9%, PARTNER 1A 9.3%, CoreValve High-Risk 13.6%, PARTNER 2 10.4%, SURTAVI 12.2%, NOTION 11.3%, PARTNER 3 3.6%, Evolut Low Risk 2.4%, UK TAVI Trial 4.6%, UK TAVI Registry 2.3% d. 30-day major vascular complications: STACCATO 2.9%, PARTNER 1A 11.0%, CoreValve High-Risk 5.9%, PARTNER 2 7.9%, SURTAVI 6.0%, NOTION 5.6%, PARTNER 3 2.2%, Evolut Low Risk 3.8%, UK TAVI Trial 4.4%, UK TAVI Registry 2.3% e. 30-day moderate to severe paravalvular leak: STACCATO 13.0%, PARTNER 1A 12.2%, CoreValve High-Risk 9.0%, PARTNER 2 3.8%, SURTAVI 3.4%, NOTION 15.3%, PARTNER 3 0.8%, Evolut Low Risk 3.4%, UK TAVI Trial 2.4%, UK TAVI Registry 3.0% f. 1 year mortality: PARTNER 1A 24.2%, CoreValve High-Risk 14.2%, PARTNER 2 12.3%, SURTAVI 6.7%, NOTION 4.9%, PARTNER 3 1.0%, Evolut Low Risk 2.4%, UK TAVI Trial 4.6% g. 1 year stroke: PARTNER 1A 6.0%, CoreValve High-Risk 8.8%, PARTNER 2 8.0%, SURTAVI 5.4%, NOTION 2.9%, PARTNER 3 1.2%, Evolut Low Risk 4.1%, UK TAVI Trial 5.0%	TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The UK TAVI trial data are not yet published in a peer-reviewed journal and as such could not be included in the guideline review. Making an exception for this study would mean inconsistency between the approach on this and other reviews because we have not sought other abstracts. Also, we note that TAVI UK trial will be limited to 1 year follow up at present, and we have sufficient published data with longer-term follow-up.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve for Life UK	Evidence Review H	133	005 - 009	The use of older data including some inappropriate data, and the exclusion of some more contemporary data, means that the relative outcomes of TAVI compared to surgery stated in the Evidence Review are not reflective of contemporary data. Specifically:- a. The Evidence Review states that there is a signal of harm for mortality for TAVI at 12 months. However, all of the 3 most recent trials (PARTNER 3, Evolut Low Risk, UK TAVI) showed lower 12-month mortality with TAVI than surgery. Published meta-analyses have also consistently shown lower 12-month mortality with TAVI. The Evidence review includes some previous meta-analyses, but has excluded published meta-analyses of the trials of TAVI vs SAVR for Low surgical risk patients. These published meta-analyses all show superior 1-year outcomes for TAVI. There is no reason for them to have been excluded. Furthermore, the Committee's own meta-analysis in the Economic model shows a very strong trend for reduced 12-month mortality, even though it has excluded data from Evolut Low-risk and UK-TAVI, both of which were associated with numerically reduced 12-month mortality for TAVI vs SAVR. b. The Evidence Review states that there is a signal of harm for TAVI with re-hospitalisation. Both PARTNER 3 and Evolut Low Risk showed substantially and significantly reduced hospitalisation at 12 months for TAVI. The Evidence review has not included the Evolut Low risk data. The Evolut Low risk trial publication includes the incidence of re-hospitalisation for heart failure at 12 months, which	Thank you for your comment. Evidence review H includes the longest possible follow-up from each study (up to 6 years for mortality outcomes) and is not restricted to 12 months. Published meta-analyses that were excluded were used to identify studies relevant to this review and all relevant studies in the low-risk population were included in evidence review H. The health economics analysis took a different approach as we were interested to capture short-term mortality benefits to assess cost-effectiveness. Hence, we looked at mortality benefits at 1 and 2 years and assumed no benefit in the long-term, as found in the clinical review. We note also that the risk ratios or hazard ratios did not suggest large differences between the two groups for these outcomes but the committee considered any difference in mortality

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				is 6.5% for surgery vs 3.2% for TAVI. The Evidence review has chosen not to include this for reasons that are unclear	based on the absolute risk difference to be important. This is described in the methods chapter, section 2.7. Subsequent paragraphs in this section also describe the uncertainty in the results for most outcomes, including mortality, and explains that no major differences between the two groups were considered to be present for most outcomes and the role health economic modelling had in the decision process. The Evolut low risk trial has now been included in the comparison of 'TAVI vs standard surgery' in the clinical review and in the economic model, owing to evidence provided by another stakeholder clarifying that only a minority had minimally invasive surgery. It had previously been analysed separately because the invasiveness of surgery was unclear. We have revised the economic model based on stakeholder comments and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline.
Valve for Life UK	Guideline	005	004	Excess waiting times for patients with severe symptomatic aortic stenosis cause avoidable harm. The prognosis of untreated severe aortic stenosis is worse than most cancers. Published data have shown a mortality of 4% per month among patients awaiting aortic valve intervention (Malaisrie 2014). Data published by Valve for Life (Ali, OpenHeart 2021) from 23 centres in the NHS demonstrated an average wait from referral to TAVI of 20 weeks, with 313 deaths in the calendar year 2019 in patients awaiting TAVI in those centres. The NICE draft guidance does not address time to assessment and time to treatment sufficiently. Valve for Life has recommended that all patients with severe symptomatic aortic stenosis should have expert assessment within 2 weeks (similar to	Thank you for your comment. Recommendation 1.1.3 has been changed and now refers to within two weeks

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				rapid heart failure assessment, rapid access chest pain clinic and suspected cancer) and not 4 weeks as stated in the guidance (page 5, line 4), and should receive definitive treatment by TAVI or surgery within 8 weeks of referral. We believe NICE should advocate similar time-to-treatment targets	
Valve for Life UK	Guideline	012	003 - 005	We completely disagree with the draft recommendation that all patients with severe aortic stenosis should be offered surgery as first-line treatment, with TAVI considered only for patients who are unsuitable for surgery with non-bicuspid anatomy. This Recommendation is wholly inappropriate. It appears to have arisen from a misunderstanding of the current clinical context of the treatment of severe AS by TAVI, from a poorly constructed evidence review, and from a highly flawed economic model. We will set out in detail below the specific reasons why we believe that the draft recommendations on intervention for aortic stenosis by TAVI or surgery are wrong.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Thank you for your comment. These points have been addressed in the subsequent comment boxes below.
Valve for Life UK	Guideline	012	003 - 005	The Recommendation is in complete contradiction to international guidelines.	Thank you for your comment. We have revised the economic model based on stakeholder comments and

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The 2017 European Society of Cardiology & European Association of Cardiothoracic Surgery guidelines give TAVI a Class 1 indication for patients unsuitable for surgery, and for patients at high and intermediate surgical risk "with TAVI favoured in elderly patients suitable for trans-femoral access". These Guidelines were produced before the publication of the Low-risk trials, and are due to be updated later in 2021, when they are likely to approve TAVI in low surgical risk patients. The 2020 American College of Cardiology / American Heart Association guidelines give a Class 1 indication for TAVI, specifically recommending that trans-femoral TAVI is preferred to surgery in patients aged over 80, or younger with a life-expectancy of 10 years or less, and that in patients who are 65 to 80 years of age and who have no contra-indication to trans-femoral TAVI, either TAVI or surgery is recommended based on shared decision-making.	have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. The recommendations made by the committee are based on the most up to date clinical and cost effectiveness evidence meeting the review protocol criteria (see Appendix A). Committee members interpret this evidence alongside their clinical experience and existing guidelines are not a source used to draft NICE guidelines. All evidence relevant to the review protocol is included and reviewed for interpretation.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve for Life UK	Guideline	012	003 - 005	The recommendations do not take any account of individual patient considerations, in particular age, life expectancy, frailty, co-morbidity, anatomical suitability for trans-femoral TAVI, and how these factors influence the best treatment options for patients.	Thank you for your comment. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Valve for Life UK	Guideline	012	003 - 005	The recommendation does not include appropriate reference to the role of the multi-disciplinary Heart team (MDT), and shared decision-making. The importance of the MDT is emphasised in all national and international guidance, including the British Heart Valve Society publication 'Network based care for heart valve disease' (2020), GIRFT Cardiothoracic Surgery	Thank you for your comment. The clinical and cost effectiveness of MDTs was not included in the scope of the guideline. However, the committee acknowledge their

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				report (2018), and ESC/EACTS 2017 & ACC/STS 2020 guidelines, as well as the NICE TAVI IPG (2017). Heart team decision-making allows complex individual patient factors such as those outlines in point 2 above to be considered. We believe that the Recommendation should be altered to refer to the importance of the MDT in deciding between TAVI and SAVR.	importance. We have therefore added the terms 'specialist assessment and advice' to the section 'terms used in this guideline' and cite MDTs as an example of how this may be provided.
Valve for Life UK	Guideline	012	003 - 005	The Recommendation is inconsistent with current clinical practice. TAVI is currently in widespread use across the NHS in patients who are suitable for surgery, and who may be categorised as high risk, intermediate risk, and even low risk, but in whom assessment of the individual patient by the MDT, based on age, life-expectancy, co-morbidities, and anatomy, leads to a recommendation of TAVI. For example, across the NHS TAVI would be considered first-line therapy for the following groups: Patients aged 80 or over, patients with frailty, patients with cognitive impairment, patients who have undergone previous cardiac surgery, patients with liver disease, patients with severe kidney disease etc. In contrast to this reality, the draft consultation states that "The committee agreed that TAVI is usually reserved for when surgery is not suitable. The guidelines therefore reflect current clinical practice". This is totally inaccurate. For at least 10 years TAVI has been used widely in patients who would have been considered operable, but high risk. For at least 5 years TAVI has been used in intermediate risk patients, and more recently also for low risk patients, IF the patient is aged at least 75 or older, and IF the patient is anatomically suitable for low-risk non-bicuspid trans-femoral TAVI. This change has been driven by trial evidence, by heart team decision-making, and by patient preference. This reality is reflected in the	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				increase in TAVI numbers from 2007 to the present day. BCIS data show a 20-30% annual increase in TAVI procedure numbers, from 66 in 2007, to 781 in 2010, 2516 in 2015, and 6076 in 2019-20, despite NO change in the mean patient age. TAVI has increased through appropriate heart team guided recommendation of TAVI in low and intermediate risk older patients.	various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Valve for Life UK	Guideline	012	003 - 005	The Recommendation would have an enormous and highly detrimental impact on clinical practice. If the proposed guidance were to be followed, there would be a huge fall in the numbers of patients having TAVI, and a huge increase in the numbers of patients having surgery. It would not be possible for surgery to deliver the increased demand, especially in the COVID and post-COVID era, and patients would face huge waits and many would die on the waiting list. Published registry data show that the mortality on a waiting list for surgery is about 4% per month. (Malaisrie, Ann Thorac Surg 2014)	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					NICE and NHSEI have published a joint implementation strategy alongside the guideline. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Valve for Life UK	Guideline	012	003 - 005	The draft guideline misjudges the impact that would occur if TAVI were to be recommended in patients suitable for surgery. Firstly, as stated above, TAVI is already frequently undertaken in patients suitable for surgery. Secondly, the guideline correctly states that 80% of surgery is in low-risk patients. However, the implication that most or many of these patients would have TAVI if it were recommended is wrong. Surgery is mostly undertaken in very low risk and much younger patients. Average age in the UK is 63 from SCTS published data, whereas average age for TAVI in the UK is 81 (UK TAVI Registry data). In line with international guidelines, TAVI	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				would only be undertaken in low-risk patients over the age of 70-75 and who are suitable for low-risk trans-femoral TAVI for non-bicuspid disease.	for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Decisions about which interventions to recommend were made based on a discussion of the available clinical and economic evidence available for each intervention. Recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.
Valve for Life UK	Guideline	012	003 - 005	The draft guideline gives no consideration to patient experience and patient preference. TAVI is performed under local anaesthetic, has a median hospital stay of 2-3 days, and immediate recovery. Surgery is highly invasive, involving chest incision, general anaesthetic, intensive care stay, median stay of 8 days in total, and recovery period of 3-6 months, especially in older patients. TAVI is therefore a far preferable experience for patients. Patient preference should always be a factor in clinical decision-making.	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for people at intermediate or low surgical risk (1.5.3). NICE and NHSEI have published a joint implementation strategy alongside the guideline. Recommendations under 'decisions about interventions' emphasise the importance of shared decision making, stating that there should be a discussion with the person about various factors, including risks of the procedure, benefits to quality of life (short and long term, capturing age and life expectancy), valve durability, possible need for future cardiac procedures and type of surgery access, and also references the NICE patient experience guideline. However, recommendations for interventions could not be made for particular populations if the cost-effectiveness analysis indicated that they were not cost-effective within that population.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Valve for Life UK	Guideline	012	003 - 005	The committee did not include any patient representation. Patients should be at the centre of guidelines and decision-making in the NHS. The failure to include patient representation may explain the failure to give sufficient focus to patient preference and patient experience	Thank you for your comment. There were two lay representatives on the committee and the guideline was produced in accordance with NICE policy on patient and public involvement https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/public-involvement-programme/patient-public-involvement-policy. The committee agree that that shared decision making is key and we specifically refer to this in recommendations 1.5.1 and 1.9.1.
Valve for Life UK	Guideline	012	003 - 005	The recommendation would be of particular harm to patients in the context of COVID. TAVI has substantial advantages over SAVR in the COVID and post-COVID era, since there is no requirement for ICU, and hospital stay is far shorter. This is reflected in the much greater fall in the numbers of SAVR cases done in 2020 than the fall seen for TAVI. This fall also means that the backlog of patients requiring treatment for severe AS is substantial. Between March and October 2020 in the UK there were 3196 fewer SAVRs than expected, and 1431 fewer TAVIs. (Martin et al. Circ Intervent. In press) If the proposed guidelines were to be implemented, the massive reduction in TAVI numbers and required increase in SAVR numbers would be impossible to deliver. Even if it were theoretically possible to do this, the	Thank you for your comment. We have revised the economic model based on stakeholder comments and have changed the recommendations. TAVI is now recommended for people at high surgical risk or if surgery is unsuitable (1.5.4) but it was not cost effective at the current valve list price for people at intermediate or low surgical risk (1.5.3).

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				increase in ICU usage would have hugely negative implications in hospitals where ICU capacity is under enormous pressure. In contrast, TAVI allows patients to be treated quickly, with short hospital stays, and no use of ICU.	NICE and NHSEI have published a joint implementation strategy alongside the guideline. NHS services are adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. This is an evolving situation and so the recommendations remain based on where evidence demonstrates interventions are clinically and cost effective. Implementation of these should take the current context into account.
Valve for Life UK	Guideline	012	006-007	The draft guideline allows no recommendation for TAVI in patients with bicuspid anatomy who are unsuitable for surgery. This is inappropriate. Although randomised trials did not include bicuspid disease, there is a substantial body of evidence from registries evaluating TAVI in bicuspid disease. For example, Forrest (2020) reported outcomes of tricuspid versus bicuspid disease treated by TAVI in the TCT registry, and showed no difference in mortality or stroke at 30 days or 12 months. TAVI in bicuspid anatomy is in routine use in the NHS. Medical therapy for AS is associated with very poor survival.	Thank you for your comment. The recommendation was limited to the non-bicuspid aortic stenosis population as this was the population covered in the included study. In addition, it was noted that TAVI is more difficult in bicuspid aortic stenosis and is not performed widely

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				TAVI should be recommended in preference to medical therapy for bicuspid disease.	currently, meaning evidence should not be extrapolated.
Valve for Life UK	Guideline	013	018	The recommendation for surgical mitral valve repair or replacement to treat isolated secondary functional mitral regurgitation is not supported by evidence, international guidelines and is not standard UK practice. Although mitral valve repair or replacement is recommended for treatment of significant functional MR for patients undergoing concomitant revascularisation, repair is associated with a significant risk of recurrence (up to 30% at 2 years), and no survival benefit is seen with either technique. Outside of the setting of coronary revascularisation the treatment of isolated functional mitral regurgitation with surgical repair or replacement is very rarely performed, and there is no evidence basis to support this. The suggestion that surgical treatment is an established and preferred option in this setting is incorrect. Given that secondary mitral regurgitation is the result of chronic left ventricular remodelling the recommendation should instead concentrate on the important of optimisation with guideline -directed medical therapy as first line treatment, and reserve both percutaneous and surgical treatment as second-line therapies. In contrast to the dearth of surgical data, a symptomatic and survival benefit was seen with percutaneous edge to edge repair (Mitraclip) in a sub-set of patients with functional mitral regurgitation in the COAPT study. This should be recommended as a potential treatment option in	Thank you for your comment. We have edited the recommendation (1.5.11) and now make it clear that it is when the person is undergoing cardiac surgery for another condition. Furthermore, the committee noted that secondary mitral regurgitation is not only the LV-secondary mitral regurgitation you refer to, but also atrial-secondary mitral regurgitation that is treated in isolation as well and with excellent results.

Heart valve disease presenting in adults: investigation and management
Consultation on draft guideline - Stakeholder comments table
16/03/21 to 29/04/21

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				symptomatic patients who are on optimal medical therapy and fulfil COAPT criteria for percutaneous mitral repair. The decision to treat patients with secondary MR with medical therapy, surgery or percutaneous edge to edge repair should be made by an appropriately represented MDT, to ensure shared decision making, and this should be reflected in the guideline.	

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*

References from Edwards Lifesciences

[3] - Baron et al. Effect of SAPIEN-3 Transcatheter Valve Implantation on Health Status in Patients with Severe Aortic Stenosis at Intermediate Surgical Risk: Results from the PARTNER S3i Trial. JACC Cardiovasc Interv. 2018 ; 11(12): 1188–1198.

[4] - Kodali et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. European Heart Journal 2016 ; 37, 2252–2262.

[5] - Thourani et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016 ; 387(10034):2218-25.

[6] - Hermann et al. One-Year Clinical Outcomes With SAPIEN 3 Transcatheter Aortic Valve Replacement in High-Risk and Inoperable Patients With Severe Aortic Stenosis. Circulation. 2016;134:130–140.

[7] - Ferlini et al. Transcatheter aortic valve replacement versus surgery in low-risk patients: a meta-analysis of randomized studies. J Cardiovasc Med 2020, 21:168–170.

[8] -Barili et al. Mortality in trials on transcatheter aortic valve implantation versus surgical aortic valve replacement: a pooled meta-analysis of Kaplan–Meier-derived individual patient data. Eur J Cardiothorac Surg 2020; doi:10.1093/ejcts/ ezaa087.

[9] - Takagi et al. Network meta-analysis of new-generation valves for transcatheter aortic valve implantation. Heart and Vessels 2019; 34: 1984–1992.

[10] - Kolte et al. Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. JACC 2019; 74(12): 1532-40.

[11] - Siontis et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. European Heart Journal (2019) 40, 3143–3153.

[12] - Leon et al. Outcomes 2 Years After Transcatheter Aortic Valve Replacement in Patients at Low Surgical Risk. JACC 2021; 77(9): 1149-61.

[13] - Arai et al. Comparison of Edwards SAPIEN 3 versus SAPIEN XT in transfemoral transcatheter aortic valve implantation: Difference of valve selection in the real world. J Cardiol 2017; 69(3):565-569.

[14]- Ando et al. Sapien 3 versus Sapien XT prosthetic valves in transcatheter aortic valve implantation: A meta-analysis. International Journal of Cardiology 2016; 220:472–478.

[15] - Kodali SK. SAPIEN 3 Transcatheter Aortic Valve Replacement Compared with Surgery in Intermediate-risk Patients: A Propensity-Matched Analysis of 5-year Outcomes. 2020 juin 21; TVT Connect 2020

[16]- Pibarot et al. Structural Deterioration of Transcatheter Versus Surgical Aortic Valve Bioprostheses in the PARTNER-2 Trial. JACC 2020; 76(16):1830-43

[17] - Blackman DJ, Saraf S, MacCarthy PA, et al. Long-Term Durability of Transcatheter Aortic Valve Prostheses. Journal of the American College of Cardiology. 2019;73(5):537-545.

[18]- Durand E, Sokoloff A, Urena-Alcazar M, et al. Assessment of Long-Term Structural Deterioration of Transcatheter Aortic Bioprosthetic Valves Using The New European Definition: A Multicenter French Study. Structural Heart. 2019;3(sup1):119-119.

[19] - Sathananthan J, Hensey M, Landes U, et al. Long-term durability of transcatheter heart valves: insights from bench testing to 25 years. JACC: Cardiovascular Interventions. 2020;13(2):235-249.

[20] - Sathananthan J, Lauck S, Polderman J, et al. Ten year follow-up of high-risk patients treated during the early experience with transcatheter aortic valve replacement. Catheterization and Cardiovascular Interventions. 2021;97(3): E431-E437.

[21] - Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. (Lancet 2016 ; 387(10034):2218-25)

[22] - Herrmann HC, Thourani VH, Kodali SK, Makkar RR, Szeto WY, Anwaruddin S, et al. One-Year Clinical Outcomes With SAPIEN 3 Transcatheter Aortic Valve Replacement in High-Risk and Inoperable Patients With Severe Aortic Stenosis. Circulation. 12 juill 2016;134(2):130-40.

[23] - Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607

[24] - Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198

[25]- Webb JG, Doshi D, Mack MJ, Makkar R, Smith CR, Pichard AD, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. *JACC Cardiovasc Interv*. 2015;8:1797–1806.

[26]- Deharo et al. Impact of Sapien 3 Balloon-Expandable Versus Evolut R Self-Expandable Transcatheter Aortic Valve Implantation in Patients With Aortic Stenosis: Data From a Nationwide Analysis. Circulation 2020;141(4):260-268.

---

[27] - Van Belle et al. Balloon-Expandable Versus Self-Expanding Transcatheter Aortic Valve Replacement: A Propensity-Matched Comparison From the FRANCE-TAVI Registry. Circulation 2020; 141(4):243-259

[28] - Thiele et al. Comparison of newer generation self-expandable vs. balloon-expandable valves in transcatheter aortic valve implantation: the randomized SOLVE-TAVI trial. Eur Heart J. 2020;41(20):1890-1899.

[29] - Kooistra et al. Randomised comparison of a balloon-expandable and self-expandable valve with quantitative assessment of aortic regurgitation using magnetic resonance imaging. Neth Heart J. 2020;28(5):253-265.

[30] - Lanz et al. Safety and efficacy of a self-expanding versus a balloon-expandable bioprosthesis for transcatheter aortic valve replacement in patients with symptomatic severe aortic stenosis: a randomised non-inferiority trial. Lancet 2019; 394: 1619–28.

[31] - Tamburino et al. Comparison of Self-Expanding Bioprostheses for Transcatheter Aortic Valve Replacement in Patients With Symptomatic Severe Aortic Stenosis SCOPE 2 Randomized Clinical Trial. Circulation. 2020;142:2431–2442.

[32] - Makkar et al. Self-expanding intra-annular versus commercially available transcatheter heart valves in high and extreme risk patients with severe aortic stenosis (PORTICO IDE): a randomised, controlled, non-inferiority trial. The Lancet 2020; 396(10252): 669-683.

[33] - Tummala R, Banerjee K, Sankaramangalam K, Mick S, Krishnaswamy A, White J, et al. Clinical and procedural outcomes with the SAPIEN 3 versus the SAPIEN XT prosthetic valves in transcatheter aortic valve replacement: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 1 sept 2018;92(3):E149-58.

[34] - Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. The Lancet. mai 2016;387(10034):2218-25.

[35] - Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J. 7 oct 2019;40(38):3143-53

[36]- French CNEDIMTS (National Commission for the Evaluation of the Medical Devices and Healthcare Technologies) 16 March 2021 – assessment of the EDWARDS SAPIEN 3, aortic valve bioprosthesis implanted by transfemoral access route (COMMANDER system): https://www.has-sante.fr/upload/docs/evamed/CNEDIMTS-6294_EDWARDS_SAPIEN3_16_03_2021_(6294)_avis.pdf

[37] - Zhou et al. Cost-effectiveness of transcatheter aortic valve implantation compared to surgical aortic valve replacement in the intermediate surgical risk population. International journal of cardiology

2019; 294: 17-22.

[38] - Pinar et al. Análisis coste-efectividad del implante transcatéter de válvula aórtica, SAPIEN 3, en pacientes con estenosis aórtica grave sintomática. Rev Esp Cardiol. 2021.

[39] - Zhou et al. Cost-Effectiveness of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients With Severe Aortic Stenosis. Heart, Lung and Circulation 2020.

[40] - Jawitz et al. Reoperation after transcatheter aortic valve replacement: an analysis of the Society of Thoracic Surgeons database. Cardiovascular Interventions 2020; 13.13: 1515-1525.

[41] - Kothapalli et al. Uncertainty in Uncertainty: How Risky Is Surgical Aortic Valve Replacement After TAVR?." Cardiovascular Interventions 2020; 13.16: 1964-1965.

[42] - Deharo et al. Transcatheter valve-in-valve aortic valve replacement as an alternative to surgical re-replacement. *Journal of the American College of Cardiology 2020; 76*(5), 489-499.

[43] - Tam et al. Transcatheter ViV versus redo surgical AVR for the management of failed biological prosthesis: early and late outcomes in a propensity-matched cohort. *Cardiovascular Interventions* 2020; 13.6: 765-774.

[44] - Adams et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. NEJM 2014; 370.19: 1790-1798.

[45] - Leon et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. NEJM 2016; 374.17: 1609-1620.

[46] - Reardon et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. NEJM 2017; 376.14: 1321-1331.

[47] - Mack et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. NEJM 2019; 380.18: 1695-1705.

[48] - Thyregod et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. JACC 2015; 65.20: 2184-2194.

[49] - Martin et al. Relative survival after transcatheter aortic valve implantation: how do patients undergoing transcatheter aortic valve implantation fare relative to the general population?. Journal of the American Heart Association 2017; 6.10: e007229.

[50] - Ler et al. Structural durability of early-generation Transcatheter aortic valve replacement valves compared with surgical aortic valve replacement valves in heart valve surgery: a systematic review and meta-analysis. Journal of Cardiothoracic Surgery 2020; 15: 1-13.

[51] - Sullivan et al. Catalogue of EQ-5D scores for the United Kingdom.*Medical Decision Making* 2011; 31.6: 800-804.

[52] - Odutayo et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ 2016;* 354.

[53] - Ludman et al. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation 2015*; 131.13:1181-1190.

[54] - UK TAVI trial ACC 2020 https://www.acc.org/latest-in-cardiology/clinical-trials/2020/03/26/21/14/uk-tavi

[55] - Mohananey et al. Clinical and Echocardiographic Outcomes Following Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement: Meta-Analysis and Meta-Regression. Circ Cardiovasc Interv. 2017;10(7).

[56] - Regueiro et al. Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. Circ Cardiovasc Interv. 2016;9(5):e003635.

[57]- Ueshima et al. The interplay between permanent pacemaker implantation and mortality in patients treated by transcatheter aortic valve implantation: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 2018; 92(3) : E159-E67.

[58] - Himmels JPW, Flottorp S, Stoinska-Schneider A, Kvist BCF, Robberstad B. Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups: a health technology assessment. Report 2021. Oslo: Norwegian Institute of Public Health, 2021

[59] - HIQA (2019). HTA of transcatheter aortic valve implantation (TAVI). https://www.hiqa.ie/reports-and-publications/health-technology-assessment/hta-transcatheter-aortic-valve-implantation

[60]- Ontario Health (Quality). Transcatheter Aortic Valve Implantation in Patients With Severe, Symptomatic Aortic Valve Stenosis at Intermediate Surgical Risk. recommendation [Internet]. Toronto (ON): Queen's Printer for Ontario; 2020 Mar. 4 p. Available from: https://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/ReviewsAnd-Recommendations/Transcatheter-Aortic-Valve-Implantation-in-Patients-With-SevereSymptomatic-Aortic-Valve-Stenosis-at-Intermediate-Surgical-Risk

[61] - Ontario Health. Transcatheter aortic valve implantation in patients with severe aortic valve stenosis at low surgical risk: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2020 Nov;20(14):1–148. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/transcatheter-aortic-valve-implantation-in-patients-with-severe-aortic-valve-stenosis-and-low-surgical-risk

References for comments 16-72 – Transcatheter Aortic Valve Replacement

[1]Halim et al. Outcomes of Transcatheter Aortic Valve Replacement in Patients With Bicuspid Aortic Valve Disease. A Report From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2020;141:1071–1079.

[2] - Winter, MP., Bartko, P., Hofer, F. et al. Evolution of outcome and complications in TAVR: a meta-analysis of observational and randomized studies. Sci Rep 10, 15568 (2020). https://doi.org/10.1038/s41598-020-72453-1.