National Institute for Health and Care Excellence

IP1192 Leadless cardiac pacemaker implantation for bradyarrhythmias

IPAC 14/06/18

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS Professional	**General, evidence 3.1**	Some of the recommendations are based on guidance issued by the MHRA Expert Advisory Committee on leadless pacing, of which I am a member. Comments pertaining to this guidance will be collated and submitted to NICE separately by the EAC chair. The document provides generic guidance for implantation of leadless cardiac pacemakers. I'm not sure that this reflects the widely differing stages of development of various devices. The Medtronic Micra now has a very large evidence base consistently showing fewer implant related complications than expected with conventional transvenous devices; experience with the St Jude (Nanostim) and EBR (Wyse) devices is limited; and the Boston Scientific device has not yet started clinical implants. The safety of newer devices cannot be inferred from the demonstration of safety in older ones. Generic guidance thus risks being either unnecessarily restrictive for mature technologies or too liberal for newer ones. The consultation document correctly points out the absence of RCTs comparing leadless to conventional single chamber pacing. It is not clear whether such trials are planned, let alone ones comparing leadless single chamber pacing to conventional dual chamber pacing (which is the mode for 75% of patients). There is concern that the potential benefits	Thank you for your comments. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and efficacy. It felt that the approach undertaken for this evidence review is appropriate. The committee agrees that the majority of the evidence comes from one device. It is also aware of the different stages of development of various devices and therefore amended 3.7 as follows: *Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices.* Section 1 of the guidance states that '*For people who can have conventional cardiac pacemaker implantation, leadless cardiac pacemakers should only be used in the context of research. Further research should report the patient selection criteria and*

			of a leadless device may be perceived to outweigh the established benefit of a dual chamber device in individual cases. There is no evidence from RCTs to support this view, nor is there likely to be in the near future. Enthusiasts may start implanting leadless devices that are incapable of dual chamber pacing, contrary to evidence based guidance from international bodies and NICE. Leadless pacing should only be considered in patients with an indication for dual chamber pacing in exceptional circumstances.	*compare leadless cardiac pacemakers with conventional pacemakers. Follow-up should be for at least 5 year and outcomes should include adverse events, symptom relief, quality of life and device durability in the long term'.* Section 3.5 of the guidance states that *'The leadless cardiac pacemakers currently available are only used for right ventricular pacing and are not suitable for people who need sequential pacing or dual-chamber pacing'.*
2	Consultee 1 NHS Professional	**1.6**	Section 1.6 of the guidance advises clinicians to follow the guidance of the MHRA EAG. This guidance was principally written for industry to cover the initial dissemination of leadless pacing following CE marking. The recommendations may not be appropriate for devices that are more mature.	Thank you for your comments. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and efficacy. Section 3.7 of the guidance was amended to state that '*different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices'*. Therefore, IPAC considers that section 1.6 advising clinicians to follow the guidance of the MHRA EAG is appropriate.
3	Consultee 6 UK Regulatory Agency for medical devices (MHRA), expert advisory group (EAG)	**1.3 evidence 3.1**	*1.3 For people who could have conventional pacemaker implantation, leadless cardiac pacemakers should only be used in the context of research*. Whilst, in principle, the EAG supports this, we would feel there is a sufficient body of evidence that certain devices, specifically the Micra, can be implanted in patients	Thank you for your comments. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and

			determined by the implanting clinician which may not fall within a research setting. The advice is generic and is applied to all leadless devices. The EAG would submit that there are differing amounts of evidence for these devices. In particular, there is a greater amount of evidence for the Micra device and we are of the view that having a generic guidance which is applied to devices at different stages of development and market release is not appropriate. The data for the Micra device show that while the complications are different, the rate adverse events is lower than that associated with conventional pacemaker implantation.	efficacy. It felt that the approach undertaken for this evidence review is appropriate. The Committee has considered that there is limited evidence on the efficacy of this procedure and has recommended in section 1.1 that *'For people who can have conventional pacemaker implantation, leadless cardiac pacemakers should only be used in the context of research'*. The committee agrees that the majority of the evidence comes from one device. It is also aware of the different stages of development of various devices and therefore amended 3.7 as follows: *Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices.*
4	Consultee 6 UK Regulatory Agency for medical devices (MHRA), expert advisory group (EAG)	**General**	This advice relates to leadless cardiac pacemaker implantation for bradyarrhythmias. As such it would not appear to be transferable to the EBR Systems WiSE CRT System which is a wireless implantable device to treat heart failure. However this distinction should be made explicit in the guidance to avoid potential confusion.	Thank you for your comment. The title of the guidance clearly states that it is for bradyarrhythmias and this is defined in section 2.1 of the guidance. Only devices with a CE mark for this indication are considered in this guidance. Other similar devices with a CE mark for different indications (EBR systems to treat heart failure) are out of the remit of this guidance. The NICE interventional procedures programme does not usually consider evidence for a different indication to the one being assessed.
5	Consultee 2	**General**	"We wish to comment on the published consultation document on Leadless (Transcatheter) Cardiac Pacing. As	Thank you for your comments.

	2 NHS Professionals		consultant cardiologists who lead our regional pacemaker services we believe we are well placed to comment. We have been involved in the development and dissemination of leadless pacemakers since their commercial release. We have been closely involved in training and proctoring clinicians in their use and have between us some of the most extensive experience of the use of transcatheter pacemakers in the UK. While we recognise that this may render ourselves subject to potential conflicts of interest, equally we feel it makes us well informed and well placed to comment on your proposals. More importantly we provide a quaternary pacemaker and lead extraction service for our respective regions and are therefore exposed daily to the substantial and under recognised adverse consequences and limitations of conventional transvenous pacing. We offer the following comments: "	
6	Consultee 2 2 NHS Professionals	**Evidence 3.1**	We offer the following comments: Your review of the published literature with regard to the implantation procedure, electrical performance and safety combines the literature for both the Nanostim and Micra devices. This is inappropriate. The development, design, implant procedure, fixation mechanisms and electronic behaviour of the two devices are completely different and have outcomes specifically related to their individual characteristics. To combine this literature is no more appropriate that assessing the literature on cholesterol reduction and combining outcome data for statins and fibrates. It is certainly the case that the Nanostim device has been plagued by problems including relatively high complication rates and subsequent device advisories. This is likely to be due at least in part to the fact that Nanostim was developed by a start-up company with no major experience in the development of pacemaker technology. The same is not the case for the Medtronic Micra device. The Micra device has	The Committee considered the comments but decided not to change the guidance. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and efficacy. It felt that the approach undertaken for this evidence review is appropriate. The committee has considered published evidence on all related devices for this procedure and indication along with specialist advice, patient organisation submissions and patient commentaries and issued the draft recommendations.

			been subject to close scrutiny with two published series demonstrate low implant complications and highly satisfactory safety and electrical performance over the short to medium term.	
7	Consultee 2 2 NHS Professionals	**Evidence 3.1**	These are substantially greater than those demonstrated in the transcatheter pacing series. Your consultation document affords insufficient recognition to the clear and widely under recognised complication rates of existing transvenous devices. Numerous large series demonstrate complication rates between 8-10. The bulk of the problems associated with transvenous pacing relates to complications inherent in accessing the vasculature and the deployment of a transvenous lead, the consequences of relying on a long conductor exposed continually to the stresses of cardiac and respiratory motion and the disruption to the integument of a subcutaneous pulse generator. The development of such complications necessitates either the insertion of yet another transvenous lead (procedures demonstrated to carry even higher complication rates than first implants) or subjecting the patient to the rigours of lead extraction, a procedure that carries significant risk of mortality and important morbidity, not to say substantial cost to the health service. The vast majority of these of these challenges are potentially avoidable with transcatheter leadless pacing. Whilst the nature of the complication profiles clearly differ between transvenous and transcatheter devices it is clear that overall complication rates are lower with transcatheter leadless pacing compared to established transvenous methods. Even in relatively inexperienced hands the rates of the most important complications of transcatheter pacing (cardiac injury and tamponade) have been demonstrated to be remarkably low (0.36%) using current best practice. We believe that the quality of data is at least as good as that available for other cardiovascular technologies approved by	The IP programme issued draft guidance after reviewing the existing evidence on the safety and efficacy of this procedure. Detailed review of the evidence, which was discussed by the committee, is presented in the **interventional procedures overview**. This document is a succinct summary of the key safety and efficacy issues and is not intended to be exhaustive. The overview provides more details about individual studies that compared leadless pacemakers with historical transvenous data. The safety data reported are those, which are described in the available comparative evidence.

			NICE at a similar stage of their evolution, for example transcutaneous aortic valve implantation (TAVI) and left atrial appendage occlusion in warfarin ineligible patients.	
8	Consultee 2 2 NHS Professionals	**3.1**	Your document does not acknowledge the rapidly increasing real world experience of transcatheter leadless pacing. In excess of 18,000 Micra devices have now been implanted worldwide leading to in excess of 30,000 patient years of experience with no signal of harm above and beyond that reported in the registry data. Transcatheter pacing has been approved by European regulatory bodies and by the US Food and Drug Administration on the basis of the same data available to NICE.	Thank you for your comments. The committee considered published relevant data on leadless pacemakers. NICE IP programme manual highlights that efficacy outcomes from non peer-reviewed studies are not normally presented to the Committee. Safety data from any source is considered.
9	Consultee 2 2 NHS Professionals	**1.1, 1.4, 1.5**	You accept that transcatheter leadless pacing can (we would argue should) be considered for those for whom conventional pacing is unsuitable. This is welcome. These individuals have no alternative pacing modality available to them other than the substantial surgical intervention required to implant an epicardial pacing system: a procedure for which many such individuals will be unfit. We agree that it is imperative that long-term prospective data is acquired with regard to the performance of these devices. We agree that centres taking on such activity must be able to demonstrate success and complication rates in line with published norm.	Thank you for your comments.
10	Consultee 2 2 NHS Professionals	**1.3**	You conclude that the use of transcatheter pacing for individuals who could potentially receive a conventional device should only be done in the context of research. The nature of this research is not stated. There is already adequate evidence of the safety of the implant technique and short term performance of the device (sufficient at least to satisfy the FDA). It is our belief that requiring short term randomised studies controlled against existing transvenous leads is unnecessary in this context and would provide no	Thank you for your comments. Section 1.1 of the guidance states that *'For people who can have conventional pacemaker implantation, leadless cardiac pacemakers should only be used in the context of research.'* Section 1.3 of the guidance states *'Further research should report the patient selection criteria and compare leadless pacemakers*

			meaningful information beyond that which is already available. Thus the only research outcomes which would add value would be with regard to the long term outcomes of the device. This will potentially take in excess of 10 years to achieve. To delay the utilisation of transcatheter pacing for that long would be depriving UK patients of technology readily available to individuals elsewhere on the western world. Rather, we believe that patients eligible for either transvenous or transcatheter technology should be provided with clear and accurate information as to the uncertainties and potential benefits and detriments of the alternative technologies and be allowed to join in an informed decision with their clinician based on existing evidence rather than having technology withheld from them that would be acceptable in other equivalent countries. Outcome and follow up data should, as you suggest, (and as is already the case) be subject to audit and review through the existing NICOR database. In summary we believe the consultation document in its current form (i) inappropriately amalgamates non-comparable data regarding different devices, (ii) understates the difficulties and challenges involved with current transvenous technology and (iii) inappropriately and unnecessarily restricts the development and of an important and significant step forward in pacing technology for cardiac patients within the UK. The above comments are reflect the agreed views of: [redacted].	*with conventional pacemakers. Follow-up should be for at least 5 years and outcomes should include adverse events, symptom relief, quality of life and device durability in the long-term.'* The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and efficacy. It felt that the approach undertaken for this evidence review is appropriate and decided not to change the guidance. The committee has considered published evidence on all related devices for this procedure and indication along with specialist advice, patient organization submissions and patient commentaries and issued the draft recommendations.
11	Consultee 3 NHS professional		I am a tertiary centre cardiologist who performs leadless pacemaker implantations, and who also works in the field of pacemaker and device removal (extraction). I feel I am well placed to make valid and clinically relevant comments on some of the points made in the document. 1.The review uses evidence regarding the safety of two entirely different systems, the Nanostim and Micra devices.	Thank you for your comments. The committee considered your comments but decided not to change the guidance. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and

			Nanostim had a lot of problems that have not affected the Micra device. The Micra device has extremely good safety data in large numbers due to its superior design and it being developed by an established manufacturer of pacemaker systems. 2.Current pacemaker systems that are implanted transvenously have large complication rates (up to 10% in some large registries)- much higher than the rates in the leadless Micra series. 3.Standard Pacemakers can fail, and the leads are the weakness in the system. This means more leads implanted, or extraction, which can be risky and expensive. 4.If pacemaker systems are extracted (e.g. for infection), a leadless system can be a better option for future pacing, as the central venous options for long term pacing are compromised following extraction. 5.The "real world" data for Micra are impressive. > 18,000 Micra devices have now been implanted worldwide with > 30,000 patient years of experience with no suggestion of harm above that reported in the registry data. 6.I agree with the comments that long-term data collection is essential. This should and will be an essential criteria for centres embarking on a leadless implant programme. NICOR submission already happens and will continue to happen 7.I am pleased to see the agreement that leadless pacing should be considered when there are no other trans-venous options, certainly before embarking on surgical approaches for example. However, there are occasions when the risk/benefits of a leadless approach should be offered to the patient to make an informed decision even if the options for trans-venous system are there, just not ideal. This should be under the umbrella of informed decision making between the patient and the team of experts who can offer the therapy. One example: a 40 year old severely disabled cerebral palsy patient with learning difficulties who presents with occasional	efficacy. The committee considered all published relevant data (including registry data) on efficacy and safety data from any source. The overview provides more details about individual studies that compared leadless pacemakers with historical transvenous data. The safety data reported are those, which are described in the available comparative evidence. The committee is aware of the different stages of development of various devices and therefore amended 3.7 as follows: *Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices.*

			syncopal episodes from intermittent sinus node pauses. A pacemaker (back up device) will help and improve quality of life for patient and carers. A traditional system would result in pain over the site, leading to risk of patient instinctively touching the area and risk of infection. Also, the pain over the chest will mean lifting and handling will be compromised, and might even risk displacing the lead early in the recovery and then resulting in a re-intervention. Following a careful discussion with regard to the uncertainty of long term outcomes, a leadless device in this context is a reasonable option for this patient. To conclude, in my opinion, this document for consultation a)does not analyse the safety data accurately of fairly, combining outcomes for two entirely different device systems b)does not pay enough attention to the problems that exist with current standard pacemaker devices and that these problems can be avoided by leadless devices c)potentially will result in this important technology not being be offered to UK patients who would benefit from it.	
12	Consultee 4 2 NHS professionals	**Lay description**	Page 1, Box 1, Lines 8-9 Remove chest pain as a symptom improved by pacing, and perhaps include exercise restriction and syncope (or black out) in addition to dizziness.	Thank you for your comments. IPAC amended the following sentence in the lay description: *The aim is to help the heart beat at a normal rate and reduce symptoms such as dizziness, shortness of breath, tiredness and fainting.*
13	Consultee 4 2 NHS professionals	**1.1**	This consultation needs to recognise that the evidence base for the two right ventricle leadless pacemakers differ. The Micra device in particular has a good evidence base showing patient safety with a large number of devices implanted both nationally and internationally. The complications cannot be looked at in isolation because there are complications associated with traditional pacemakers. Complications such as lead or device displacement and early pacemaker	Thank you for your comments. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and efficacy. The committee considered all published relevant data (including registry

			infection are likely to be lower with a Micra than with a traditional system (displacement 0.13% in the Micra Transcatheter pacing system post-approval Registry, vs 0.3% RV lead dislodgement rate or Infection 1% vs 0.13% Ghani et al 2014).	data) on efficacy and safety data from any source for this procedure. The overview provides more details about individual studies that compared leadless pacemakers with historical transvenous data. The safety data reported are those, which are described in the available comparative evidence. The committee is aware of the different stages of development of various devices and therefore amended 3.7 as follows: *Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices.*
14	Consultee 4 2 NHS professionals	**1.2**	Consider relative uncertainty when compared to conventional leaded pacemaker implantation; consider mid- and long-term efficacy as per MHRA guidance.	Thank you for your comment. IPAC amended section 1.2 of the guidance as follows: • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy compared with conventional pacemaker implantation, and provide them with clear written information. In addition, the use of NICE's **information for the public** *[[URL to be added at publication]]* is recommended.
15	Consultee 4 2 NHS professionals	**1.3**	Many types of patient could have a conventional pacemaker or a leadless pacemaker. Use of a leadless pacemaker in this situation should not be restricted only to patients undergoing research studies as the relative balance of future clinical risks may favour consideration of a leadless approach	Thank you for your comments. The Committee considered this comment but decided not to change the guidance.

			e.g. in renal dialysis patients with potential future limited vascular access and post-extraction patients with an increased risk of recurrent infection. With appropriate clinical governance as per draft NICE document, informed consent and mechanisms for audit, a clinically-relevant shared-decision making approach is a reasonable.	
16	Consultee 4 2 NHS professionals	**2.2**	Multiple typographic errors exist in this paragraph with recurrent reference to combinations of sinus node dysfunction and/or atrio-ventricular block. Please consider simplification of the text to include these two entities in isolation and combination alone, stated once.	Thank you for your comments. IPAC acknowledged this error and amended section 2.2 of the guidance as follows: Bradyarrhythmias are managed with pacemakers as described in NICE's technology appraisal guidance. Dual-chamber pacing is recommended for symptomatic bradycardia caused by sick sinus syndrome, atrioventricular block, or a combination of sick sinus syndrome **and/or atrioventricular block** and, and also for sick sinus syndrome in people **without atrioventricular block**. Single-chamber ventricular pacemakers may be used for atrioventricular block alone or with sick sinus syndrome in people with continuous atrial fibrillation, or people who have specific factors such as frailty or comorbidities that influence the balance of risks and benefits in favour of single-chamber pacing.
17	Consultee 4 2 NHS professionals	**2.3**	This paragraph outlines only the basic process behind leadless pacing for bradycardia and does not include reference to the more complex technique of wireless LV pacing for CRT (WICS, EBR systems) covered in the MHRA guidance. Please consider clarification throughout the document. Screw-in deployment references the Abbott Nanostim device, which is currently unavailable. Furthermore, reference to	Thank you for your comments. The title of the guidance clearly states that it is for bradyarrhythmias and this is defined in section 2.1 of the guidance. Only devices with a CE mark for this indication are considered in this guidance. Other similar devices with a CE mark for different indications (EBR systems to treat heart failure) are out of the remit of this guidance.

			apical implantation sites should be changed as current implantation guidance for Medtronic Micra specifically avoids targeting this location.	The NICE interventional procedures programme does not usually consider evidence for a different indication to the one being assessed. The committee was aware of the different stages of development of various devices and therefore amended 3.7 as follows: *Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices.* Section 2.3 in the guidance is intended to be a broad summary of the leadless pacemaker implantation procedure rather than individual device implantation procedures. **IPAC amended 2.3 as follows:** The aim of implanting a leadless cardiac pacemaker is to detect cardiac bradyarrhythmias and deliver electric pulses to the heart to increase the heart rate. The leadless pacemaker has a built-in pulse generator, battery and electrodes. The procedure is done under local anaesthesia, with or without sedation, in a cardiac catheterisation laboratory. Under fluoroscopic guidance, the proximal end of the pacemaker is attached to a deflectable bespoke delivery catheter system and inserted percutaneously through the femoral vein using a dedicated introducer sheath. It is then advanced into the right atrium through the tricuspid valve, into the right

				ventricle and positioned near the apex or lower septum. Contrast may be injected into the right ventricle to visualise the desired location. Once positioned, the pacemaker is deployed and securely implanted into the endocardial wall using a fixation mechanism (a screw-in helix or nitinol tines). An electrode at the distal end of the pacemaker delivers electrical impulses that pace the heart. Electrical measurements are taken and, if satisfactory, the pacemaker is released from the catheter and the catheter is removed. If the position is suboptimal, the pacemaker can be detached from the endocardium and repositioned prior to final release of the delivery catheter.
18	Consultee 4 2 NHS professionals	**2.4**	This paragraph appears slightly incongruous. Pacemaker programming is referenced but then both repositioning (an acute option, prior to final release from the catheter-based implantation kit) and retrieval (a more technically challenging option, necessary only following device dislodgement after final release from the implantation kit and involving complex / variable retrieval kit). Please consider separating discussion of these issues.	Thank you for your comments. IPAC amended section 2.4 as follows: 'The pacemaker is programmed using an external programmer that transmits signals to it. The pacemaker can be retrieved using a catheter retrieval system, if device dislodgement is discovered at follow-up'.
19	Consultee 5 NHS professional	**1.1 & general**	"This is a very timely review of what will eventually be standard pacemaker technology in the future. I fully support a recommendation for implanting the Medtronic MIcra leadless pacemaker. My main comment is that the existing environment for leadless pacing is dominated by the Medtronic Micra system, which is the only currently available technology in clinical use and with highly supportive data from clinical studies and registries to support its utility and safety and a perfect record at our own centre (100% implant success and no complications in>30 cases). Therefore, in my view guidance from NICE should clearly stipulate that the other technologies	Thank you for your comments. The committee is aware of the different stages of development of various devices and therefore amended section 3.7 as follows: *Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices.*

			from St Jude and Boston are not yet ready for widespread adoption until robust data is available to support their use. But the Micra system should be given guidance for use based on what is now a large and rapidly growing worldwide experience with very encouraging safety and implant success rates. One final point relates to the number of operators per centre. With Barts being so large, now with 20 Electrophysiology and Device Consultants, we have a total of 3 Micra implanters, all with good early experience already and so although 2 operators for the vast majority of centres makes perfect sense, an exception should be made for Barts where having 3 operators is appropriate in my view and has allowed us to offer Micra as a clinical option for patients at nearly all times when required, preventing long in-hospital stays."	Section 1.5 of the guidance states that *"the procedure should only be done in specialist centres by clinicians with specific training on, and supervised experience in, inserting the device".* The committee does not have a remit to determine the number of operators per centre.
20	Consultee 7 Company (Medtronic Ltd)	**General**	There are two technologies under consideration for this Inteventional Procedure Guideline and the consequence is the guidance cannot be generalised owing to differences in the design and materials of the fixation mechanism, the pacemaker delivery system, the technique of the deployment of the pacemaker during the procedure, and differences in the electronics of the individual pacing capsules. Therefore, in line with NICE procedures gudiance we politely request that where the evidence is referenced in the recommendations, it is explicit as to which device this is relevant to.	Thank you for your comments. The IP programme issues guidance on interventional procedures rather than individual devices after having reviewed the best existing evidence on its safety and efficacy. The recommendations are not specific to any particular device. The committee is aware of the different stages of development of various devices and therefore amended 3.7 as follows: '*Different devices are available or in development for use in this procedure, and the technology and their attachment mechanisms are evolving. There is limited evidence on efficacy and safety for some of these devices'.*
21	Consultee 7 Company (Medtronic Ltd)	**1.1**	*1.1 "Evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well recognised complications"*	Thank you for your comments. IPAC does not comment about the evidence in section 1.1 and does not consider comparative effectiveness.

			As there are also serious and well recognized complications with conventional pacemakers, the informative value of this statement is limited if made in isolation. Although transvenous pacemakers are an effective and common therapy, complications occur and frequently relate to the leads or to the subcutaneous “pocket”. The Dutch nationwide FOLLOWPACE study, one of the few large studies (1,517 patients) with a relatively long mean follow-up duration (5.8 years) reported a rate of lead complications - such as dislodgement, fractures and cardiac injuries - up to 11% at five years. The rate of pocket complications (infection/pocket erosion, hematoma) at five years was estimated to be 8% in the same study.[1] Due to its design leadless pacing eliminates all complications related to lead and pocket. In matched cohort analysis complications for the Micra TPS are shown to be lower than conventional pacemaket systems: Both, the complication rates from 1817 patients in the Micra postmarket registry (2.7%) and 726 patients in the Micra IDE trial (4%) are significantly lower than the complication rate in the matched control group with conventional pacemakers (7.6%) at 12 months follow up.[2][3] In a new publication using matched cohort analysis, complications for both leadless pacemakers are shown to be lower than conventional pacemaker systems: The complication rate for leadless pacemakers from 220 patients from 3 Dutch implant centers (0.9%) is significantly lower than the complication rate in the matched control group with conventional single	

[1] Udo, E.O., N.P. Zuithoff, N.M. van Hemel, et al., Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm*, 2012. **9**(5): p. 728-35

[2]El-Chami et al, “Leadless Pacemaker Implant in Patients with Pre-Existing Infections: Results from the Micra Post-Approval Registry” Presented at the Heart Rhythm Society Congress 2018.

[3] Duray G Z, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana J M, Zhang S, Soejima K, Steinwender C, Rapallini L, Cicic A, Fagan D H, Liu S and Reynolds D 2017 Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study. *Hear. Rhythm*

			chamber pacemaker (4.7%) at 800 days follow up. The complication rate of 0.9% exclude the complications due to battery failure of Nanostim as they are expected not to be inherent to leadless pacing. Data for the transvenous single-chamber pacemaker cohort was obtained from the prospective Dutch FOLLOWPACE study. [4] The complication rate of conventional single chamber pacemakers has been estimated to be close to 7% in two large studies. In a nationwide cohort study in Denmark, the complication rate for single-chamber pacemaker patients was reported to be 6.9% at 6 months.[5] Similarly, the rate was 7.7% at 1 months in a US nationwide claims data analysis.[6] Almost 90% of complication related claims could have been avoidable by a leadless pacemaker due to the elimination of lead and pocket. Consequently, leadless pacing has the potential to overcome the serious complications which are associated with lead and pocket which can cause interruption of pacemaker therapy, hospitalization, and in some instances death. We ask the point in1.1 is revised to: • "Evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well recognised complications as is the case for conventional pacemaker systems. Evidence from matched cohort analysis indicate there is a significantly lower rate of major complications with leadless cardiac pacemakers compared to conventional pacemakers"	

[4] Tjong, Fleur VY, et al. "Leadless Pacemaker Versus Transvenous Single-Chamber Pacemaker Therapy: A Propensity Matched Analysis." Heart rhythm (2018).

[5] Kirkfeldt R E, Johansen J B, Nohr E A, Jorgensen O D and Nielsen J C 2014 Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur. Heart J.* **35** 1186–94

[6] Cantillon DJ, Exner DV, Badie, N et al. Complications and Health Care Costs Associated With Transvenous Cardiac Pacemakers in a Nationwide Assessment. J Am Coll Cardiol EP 2017 3(11): 1296-1305

22	Consultee 7 Company (Medtronic Ltd)	**1.1**	• "The evidence of efficacy is inadequate in quantity and quality" We ask the committee to reconsider revising this judgement to "adequate" and refer to: • The NICE IPG Programme manual page 26, section 9 "Evidence considered by the committee". The manual recognises that randomised controlled trials (RCTs) are often not available for medical devices. Non-randomised comparative studies, case series and case reports may therefore be the main sources of data. We also refer to the key efficacy outcomes defined by the specialist advisors which are **"adequate pacing performance and quality of life".** • Adequate Pacing Performance: a. In a case series of 725 Micra TPS study 292/297 patients with 6 months follow up exceeded the performance goal of 80% based on a comparison with a historical transvenous control group by achieving 98.3%.[7] b. In a case series of 795 patients with Micra TPS thresholds were captured from 701 patients at implant and 97% had adequate pacing thresholds of ≤ 2 .[8] c. We refer to the recommendations in IPG 603 for subcutaneous cardioverteter defibrillator insertion for preventing sudden cardiac death. The evidence for efficacy of this procedure is considered to be "adequate" both in the recent update in 2017 and previously in the original recommendation in 2013. Evidence for this	Thank you for your comments. The committee considered all published evidence (including registry data) on efficacy and safety data from any source for this procedure. The wording 'inadequate in quantity and quality' is the judgement of the committee, and is consistent with other guidance produced by the committee. Studies reporting adequate pacing performance referenced by the consultee (Reynolds 2016, Roberts 2017) are included in table 2 in the overview. Although IPG603 considered the evidence on efficacy is adequate, for this draft guidance the committee felt that the evidence on efficacy is inadequate in quality and quantity. The Committee felt that longer term follow-up data was required particularly in the context of a condition for which there are alternative established treatment options for management. The Committee thought that the balance between the invasiveness of the procedure, its safety and its efficacy still demanded more data and longer-term evidence. The committee considered published relevant data on leadless pacemakers. NICE IP programme manual highlights that

[7] Reynolds D, Duray G Z, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts P R, Sagi V, Hummel J, Bongiorni M G, Knops R E, Ellis C R, Gornick C C, Bernabei M A, Laager V, Stromberg K, Williams E R, Hudnall J H and Ritter P 2016 A Leadless Intracardiac Transcatheter Pacing System N.Engl.J.Med. 374 533–41

[8] Roberts, Paul R., et al. "A leadless pacemaker in the real-world setting: the Micra Transcatheter Pacing System Post-Approval Registry." Heart Rhythm 14.9 (2017): 1375-1379.

			procedure is from matched controlled (69 patients with sub Q ICD), restrospectively propensity match study (140 patients with sub Q ICD's) and prospective case series (321 patients with sub Q ICD), matched propensity controlled study (167 patients with a sub Q ICD) In the studies appraised for efficacy the numbers of patients in the Sub Q ICD studies are lower than the number of patients in the Leadless Pacemaker studies. (697 patients in the sub Q ICD series versus 998 in Micra TPS plus 559 in LCP; total of 1557 for Leadless Pacemakers) • Quality of Life Evidence on quality of life was submitted in the Structured Information Request and has not been included in the Overview. In addition, complications requiring surgical reintervention are likely to impact the quality of life of a patient temporarily as assumed in the economic model prepared for the NICE TA for cardiac resynchronisation therapy (biventricular pacing) NICE TA 314. An infection is assumed to have a greater impact on the patients quality of life which is a reasonable assumption given the need for device extraction and re-implantation and IV antibiotic therapy in addition.[9] Due to lower rates of complications with the Micra TPS compared to transvenous pacing as shown in matched cohort analysis, systems revisions are 82% lower than in the matched control group at 12 months.[10] . Importantly, no systemic infection has been reported in the Micra TPS since commercial release in June 2015. We refer you to the evidence	efficacy outcomes from non-peer-reviewed studies are not normally presented to the Committee. Safety data from any source is considered. Evidence on quality of life submitted in the Structured Information Request (Tjong, MD; Beurskens NE, de Groot JR et al. Health-Related Quality of Life Impact of a Transcatheter Pacing System Under journal review) is not yet published in a peer-reviewed journal. Therefore, it has not been included in the overview. Reference 10 (Duray 2017) has been included in table 2 in the overview.

[9] Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A and Taylor R S 2007 The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. Health Technol. Assess. 11iii–iv, ix-248

[10] Duray G Z, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana J M, Zhang S, Soejima K, Steinwender C, Rapallini L, Cicic A, Fagan D H, Liu S and Reynolds D 2017 Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study. *Hear. Rhythm*

			submitted Academic in Confidence in the SIR.Micra is fully encapsulated in fibrous tissue over time, thus removing any direct contact with blood and likely reducing the risk of long-term infections. Micra's small size, reduced surface area, and lack of polymer insulated lead exposed to the bloodstream appear to substantially mitigate the risk of early device infection[4].Reducing the risk of infection is particularly valuable for patients with chronic conditions who are at higher risk of cardiac device infections.[11] A manuscript under journal review on quality of life was provided in the Structured Information Request as Academic In Confidence. • In summary we ask the committee to reconsider the classification of the evidence for efficacy to reflect the evidence base and to change the decision to "adequate"	
23	Consultee 7 Company (Medtronic Ltd)	**1.1**	• "For people who cannot have conventional cardiac pacemaker implantation, leadless cardiac pacemakers should only be used with special arrangements for clinical governance, consent and audit or research" The above recommendation currently excludes important patient cohorts who should be considered for a leadless pacemaker implantation. There are several conditions which expose patients to a higher risk of lead or pocket complication and would therefore particularly benefit from the leadless pacemaker . Case studies/series give insights	Thank you for your comments. IPAC amended the main recommendation 1.1 as follows: • "Evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well recognised complications. The evidence on efficacy is inadequate in quantity and quality… For people in whom a conventional cardiac pacemaker implantation is contraindicated following a careful risk assessment by the multidisciplinary team, leadless cardiac pacemakers should

[11]Polyzos K A, Konstantelias A A and Falagas M E 2015 Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Eur. Eur. pacing, arrhythmias, Card. Electrophysiol. J. Work. groups Card. pacing, arrhythmias, Card. Cell. Electrophysiol. Eur. Soc. Cardiol. 17 767–77

			into the conditions that put a patient into the "high risk" category.[12][13][14][15][16][17][18][19][20][21][22] Conditions include : • Pacemaker lead failures where lead extraction is difficult or risky • Compromised venous access – Subclavian vein occlusion/stenosis due to previous conventional transvenous pacemaker implantations/revisions – Total vena cava occlusion - preservation of superior veins desired for other therapies • Bioprosthetic tricuspid valve replacement • High risk of infection The implantation of a lead and pocket would expose these patients to considerable risk and a leadless pacemaker therefore represents an important alternative. Infections for example are hazardous because they carry a 29% mortality from a lead	only be used with special arrangements for clinical governance, consent and audit or research."

[12] Da Costa A, Axiotis A, Romeyer-Bouchard C, et al. Transcatheter leadless cardiac pacing: The new alternative solution. *Int J Cardiol*. January 15, 2017;227:122-126.

[13] Muller GC, Gosau N, Arndt F, et al. Leadless Pacing by Micra Transcatheter Pacing System: First Treatment of a Congenital Heart Disease Patient as the Only Option to Avoid Heart Transplant. *Thorac Cardiovasc Surg*. 2016;64:ePP5.

[14] Kerwin SA, Mayotte MJ, Gornick CG. Transcatheter pacemaker implantation in a patient with a bioprosthetic tricuspid valve. *J Interv Card Electrophysiol*. October 2015;44(1):89-90.

[15] Garweg C, Ector J, Willems R. Leadless cardiac pacemaker as alternative in case of congenital vascular abnormality and pocket infection. *Europace*. October 2016;18(10):1564.

[16] Lau CP, Lee KL. Transcatheter Leadless Cardiac Pacing in Renal Failure with Limited Venous Access. *Pacing Clin Electrophysiol*. November 2016;39(11):1281-1284.

[17] Ferrero P, Yeong M, D'Elia E, Duncan E, Graham Stuart A. Leadless pacemaker implantation in a patient with complex congenital heart disease and limited vascular access. *Indian Pacing and Electrophysiology J*. November-December 2016;16(6):201-204.

[18] Solis LD, Toquero J, Castro V. Leadless Pacemaker Due to Bilateral Subclavian Stenosis. *Rev Esp Cardiol (Engl Ed)*. April 2017;70(4):294.

[19] Polyzos K A, Konstantelias A A and Falagas M E 2015 Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Eur. Eur. pacing, arrhythmias, Card. Electrophysiol. J. Work. groups Card. pacing, arrhythmias, Card. Cell. Electrophysiol. Eur. Soc. Cardiol. 17 767–77

[20] Lekkerkerker, Jaco C, et al. "Risk factors and time delay associated with cardiac device infections: Leiden device registry." Heart May 95(9) (2009): 715-20.

[21] Lin YS, et al. "Risk factors influencing complications of cardiac implantable electronic device implantation: Infection, pneumothorax and heart perforation: A nationwide population-based cohort study." Medicine 93:e213 (2014): 1–8.

[22] Norgaard, Mette Lykke, et al. "Suicide Attempt by Complete Self Removal of a 12-Year-Old Permanent Pacemaker System: Case Report." Journal of cardiovascular electrophysiology 25.1 (2014): 99-100.

				infection and 5% mortality risk after a pocket infection.[23] While pacemaker infections rates in the general patient population can be considered low[2425] , the infection rate is known to be significantly higher in patients with chronic conditions. The risk factors for cardiac device infection are well studied and clearly identified.[26] Often, a combination of impaired immunity coupled with the need for repeat intravascular access leads to a particularly high-risk situation as has been explained in various studies regarding renal dysfunction.[272829] In addition, cancer patients have been shown to have a general elevated risk of infection.[30]No systemic infection has been reported in the Micra TPS since commercial release in June 2015. We refer you to the evidence submitted in Academic in Confidence in the SIR. Moreover, Micra may provide an important alternative for patients with prior cardiac device infection. Micra has been implanted in 99 patients with prior pacemaker system infection without recurrent infection during	

[23] Sandoe J A T, Barlow G, Chambers J B, Gammage M, Guleri A, Howard P, Olson E, Perry J D, Prendergast B D, Spry M J, Steeds R P, Tayebjee M H and Watkin R 2015 Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rh J. Antimicrob. Chemother. 70 325–59

[24] Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey J L, Lande G, Lazarus A, Victor J, Barnay C, Grandbastien B and Kacet S 2007 Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation 116 1349–55

[25] Johansen, Jens Brock, et al. "Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients." European heart journal 32.8 (2011): 991-998

[26] Polyzos K A, Konstantelias A A and Falagas M E 2015 Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Eur. Eur. pacing, arrhythmias, Card. Electrophysiol. J. Work. groups Card. pacing, arrhythmias, Card. Cell. Electrophysiol. Eur. Soc. Cardiol. 17 767–77

[27] Morani et al, Redo procedures and chronic renal dysfunction are associated with higher risk of cardiac electronic device infections 2018, Minerva Cardioangiologica

[28] Tompkins, Christine, et al. "End-Stage Renal Disease Predicts Complications in Pacemaker and ICD Implants." Journal of cardiovascular electrophysiology 22.10 (2011): 1099-1104.

[29] Guha, Avirup, et al. "Cardiac implantable electronic device infection in patients with end-stage renal disease." Heart Rhythm12.12 (2015): 2395-2401.

[30] Blimark, Cecilie, et al. "Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients." Haematologica 100.1 (2015): 107-113.

			mean follow up of 5.5 months. Importantly, in 36.4% of these patients, Micra has been implanted in the same procedure as the extraction of the conventional device and thus the patient's therapy did not need to be interrupted.[31] We suggest the following change to the Draft Recommendation: • "For people who cannot have a conventional cardiac pacemaker implantation, and people who have an increased risk of complications with conventional pacemaker implantation, leadless cardiac pacemakers should only be used with special arrangements for clinical governance, consent and audit or research."	
24	Consultee 8 Company (Boston Scientific)	**1.1, 1.3**	We are pleased to see that NICE is evaluating the evidence on safety and efficacy with regards to leadless cardiac pacemaker implantation for bradyarrhythmia. We recognise the potential that this technology has to transform the care of patients who require pacing. We note the points made in the patient organisation submissions about how leadless pacemakers can restore a patient's quality of life, independence and ability to work and would encourage NICE to more clearly support this technology than the draft IPG currently does.	Thank you for your comments. The committee has considered published evidence on all related devices for this procedure and indication along with specialist advice, patient organization submissions and patient commentaries and issued the draft recommendations.
25	Consultee 8 Company (Boston Scientific)	**1.1**	Having carefully read the Overview document and in particular the section about the studies included we are unsure how NICE have reached the conclusion that the evidence on efficacy is inadequate. The studies included by NICE in the literature review range in size from only a small one with 33 patients, the remainder including between 500 and 1400 patients.	Thank you for your comments. The IP programme issued draft guidance after having reviewed the best existing evidence on the safety and efficacy of this procedure, regardless of which device was used. Detailed review of the evidence, which was discussed by the committee, is presented in

[31] El-Chami et al, "Leadless Pacemaker Implant in Patients with Pre-Existing Infections: Results from the Micra Post-Approval Registry" Presented at the Heart Rhythm Society Congress 2018.

			The implant success rates documented are 97%, 95.8%, 99.2% and 100%. We feel these figures alone are a sign of efficacy, certainly in terms of adequate pacing performance and they are reinforced by the figures quoted in the NICE overview document. These figures quoted there include statistically significant improvements in pacing performance from implantation to 12 months and achievement of 93% acceptable pacing performance against a goal of 80%. We acknowledge that figures quoted for repositioning of the device appear to be high but feel these are tempered by the high implant success rates quoted above.	the **interventional procedures overview** . This document is a succinct summary of the key safety and efficacy issues and is not intended to be exhaustive. The wording 'inadequate in quantity and quality' in 1.1 is the judgement of the committee, and is consistent with other guidance produced by the committee.
26	Consultee 8 Company (Boston Scientific)	**1.1 – 1.3**	In the draft recommendations leadless cardiac pacemakers are compared to conventional pacemakers, in fact, their potential use depends on whether the patient can or cannot have a conventional cardiac pacemaker. Therefore, for the evaluation of the safety of this procedure we would ask NICE to also highlight the potential for complications of conventional pacemakers as shown in the literature (Moazzami K et al. 2017 http://dx.doi.org/10.1016/j.jacep.2016.05.009). In addition, having carefully read the Overview document and in particular the section about the studies we feel that some data support the safety of this procedure. For this reason, we have listed below some figures we feel show this: Reddy VY had a complication free rate of 94%, one death and 0 device related events. Reynolds D found an overall device or procedure related major complication free rate of 96% at 12 month compared with a safety performance goal of 83%, which was based on historical transvenous control data.	Thank you for your comments. The IP programme issued draft guidance after having reviewed the best existing evidence on the safety and efficacy of this procedure, regardless of which device was used. Detailed review of the evidence, which was discussed by the committee, is presented in the **interventional procedures overview** . This document is a succinct summary of the key safety and efficacy issues and is not intended to be exhaustive. The overview provides more details about individual studies that compared leadless pacemakers with historical transvenous data. The safety data reported are those, which are described in the available comparative evidence.

			Reddy VY - study 2 - found that whilst 6.5% of patients suffered a device or procedure related serious adverse event by 6 months the prespecified performance goal of 86% had been exceeded as 93% of patients were free from the events. Reynolds D found that when compared to 2667 patients in a control group, major complications were at 4% vs 7.6%, Death 0.1% vs 0, Hospitalisations 2.3% vs 4.1%, Prolonged hospitalisations 2.2% vs 2.4% & system revisions 0.7 %to 3.8%. Perhaps most importantly rates of fixation related events were statistically significantly higher in the control cohort than the use of TPS. Roberts PR similarly found device related major complications at 1.5%. There were 21 cases of perforation, tamponade or effusion reported across all studies (2079 patients in total). No study reported vascular complication rates higher than 1.2% There was very low incidence of DVT reported. Device dislodgement and migration together with elevated pacing thresholds that needed retrieval and replacement were all reported at less than 1% of patients.	
27	Consultee 8 Company (Boston Scientific)	**1.1**	*Evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well recognised complications. The evidence on efficacy is inadequate in quantity and quality.* Despite some limitation in the evidence on safety and efficacy of this procedure, we would like to highlight that all devices available in Europe have a CE Mark, which	Thank you for your comment. The wording 'inadequate in quantity and quality' in 1.1 is the judgement of the committee, and is consistent with other guidance produced by the committee.

			demonstrates that they can achieve the intended level of performance whilst also giving patients and users a high level of protection. We recognise that outcomes are also determined by the experience of the clinical team and patient comorbidity and would suggest that if NICE wish to retain this statement about safety and efficacy that NICE should make such a differentiation.	
28	Consultee 8 Company (Boston Scientific)	**1.3**	We agree that follow up should be for at least 5 years and the outcomes listed included in the registry.	Thank you for your comments.
29	Consultee 8 Company (Boston Scientific)	**1.5**	We agree and particularly believe in the importance of rigorous training to ensure the best health outcome for the patient. Therefore, we would suggest NICE to add the following sentence to this section: *Physician and healthcare professional training are key safety features. Manufacturers have adopted varied training programmes and physician training to proficiency mitigates procedure-learning related risk and exposes patients only to unavoidable clinical risks that cannot be mitigated.*	Thank you for your comments. IPAC added a committee comment in section 3.8 as follows: *The committee was informed that different manufacturers offer different types of training programmes.*
30	Consultee 8 Company (Boston Scientific)	**2.3**	We would like to emphasize that the delivery system design and ergonomics of the device are critical for safe execution of the implant procedure. Therefore, we would suggest that NICE amend this paragraph as follows: The aim of implanting a leadless cardiac pacemaker is to detect cardiac bradyarrhythmias and deliver electric pulses to the heart to increase the heart rate. A leadless pacemaker is introduced into the right heart chambers via (usually femoral) venous access using a bespoke delivery system and fixated to the endocardial wall. The leadless pacemaker has a built-in pulse generator, battery and electrodes. The procedure is done under local anaesthesia, with or without sedation, in a cardiac catheterisation laboratory.	Thank you for your comment. IPAC amended 2.3 as follows: The aim of implanting a leadless cardiac pacemaker is to detect cardiac bradyarrhythmias and deliver electric pulses to the heart to increase the heart rate. The leadless pacemaker has a built-in pulse generator, battery and electrodes. The procedure is done under local anaesthesia, with or without sedation, in a cardiac catheterisation laboratory. Under fluoroscopic guidance, the proximal end of the pacemaker is attached to a deflectable bespoke delivery catheter system and inserted percutaneously through the femoral vein using a dedicated introducer sheath. It is then advanced into

				the right atrium through the tricuspid valve, into the right ventricle and positioned near the apex or lower septum. Contrast may be injected into the right ventricle to visualise the desired location. Once positioned, the pacemaker is deployed and securely implanted into the endocardial wall using a fixation mechanism (a screw-in helix or nitinol tines). An electrode at the distal end of the pacemaker delivers electrical impulses that pace the heart. Electrical measurements are taken and, if satisfactory, the pacemaker is released from the catheter and the catheter is removed. If the position is suboptimal, the pacemaker can be detached from the endocardium and repositioned prior to final release of the delivery catheter.
31	Consultee 8 Company (Boston Scientific)	**3.1**	In the last six months, some relevant studies have been published and we would ask NICE to consider them in the review of the evidence on the safety and efficacy of leadless cardiac pacemaker implantation. Leadless pacemaker versus transvenous single chamber pacemaker therapy: a propensity matched analysis. Tjong et.al., Heart Rhythm, 2018, April 27 (635 patients, of which 254 leadless and 381 transvenous) Safety and feasibility of leadless pacemaker in patients undergoing atrioventricular node ablation for atrial fibrillation. Yarlagadda et.al., Heart Rhythm 2018, Mar 1 (127 patients, of which 60 leadless and 67 transvenous) Mid-term safety and performance of a leadless cardiac pacemaker system: 3 year follow-up to the LEADLESS trial. Tjong et.al. Circulation 2018, Feb. 6 (33 patients)	Thank you for your comments. The following articles in press (Tjong 2018 Yarlagadda 2018, Tjong 2018,) have been added to table 2. Okabe 2018 has been added to appendix in the overview. Sperzel 2018 has been added to table 2. Boveda 2018 is an online survey on the current use of leadless pacemakers and has been added to appendix in the overview.

			Leadless pacemaker implantation and concurrent atrioventricular junction ablation in patients with atrial fibrillation. Okabe et.al., Pacing Clin. Electrophysiology, 2018, Feb. 24 (21 patients, retrospective) Primary safety results from the LEADLESS Observational study. Sperzel et.al. Europace 2018, Jan. 19 (safety data on 300 Nanostim devices, data on 470 enrolled patients) Use of leadless pacemakers in Europe: results of the European Heart Rhythm Association survey. Boveda et.al. Europace 2018, Mar 1.	
32	Consultee 8 Company (Boston Scientific)	**3.6**	Only one paper provided data on battery failure (Lakkireddy D, 2017), which quoted battery failures in 2.3% of 1423 patients. We feel that this statement is misleading given the fact that it is based on 1 paper alone (based on one manufacturer only).	Thank you for your comment. IPAC amended section 3.6 as follows: Problems related to battery life have been reported for 1 device.
33	Consultee 9 Company (Abbott)	**1.1**	˜Special arrangements" should also apply to patients that a multi-disciplinary team decides who should have a leadless pacemaker. There may be situations in which clinicians decide that it is in a patient's best interest to receive a leadless device.	Thank you for your comment. IPAC have indicated that providers using this procedure should do so with "special arrangements" for clinical governance, consent and audit or research. This recommendation is intended to address the practical steps that clinicians should take to carry out the procedure in relation to the hospital's clinical governance arrangements, the patient consent process and the collection of data. Seection 1.1 of the guidance has been amended as follows: 'For people in whom a conventional cardiac pacemaker implantation is contraindicated following a careful risk assessment by the multidisciplinary team, leadless cardiac

				pacemakers should only be used with special arrangements'.
34	Consultee 9 Company (Abbott)	**1.3**	Please clarify whether 5-year follow up has to be specified in a research protocol or whether clinical follow up to 5 years be adequate?	Thank you for your comment. The Committee has considered that there is limited evidence on the efficacy and safety of of this procedure and recommended further research with long term follow-up. Routine data collection may be either in the form of any audit or through a register, or research in formal clinical studies to address this uncertainity and further enable NICE to review and update the guidance.
35	Consultee 9 Company (Abbott)	**1.5**	We agree with these requirements.	Thank you for your comment.
36	Consultee 9 Company (Abbott)	**3.1**	The literature review should also consider the data published by Sperzel et al Europace (2018) 0, 1-7. Mean follow up in 470 patients is 19.5 months in this publication.	Thank you for your comment. This study was identified in our update search and has been added to table 2.
37	Consultee 9 Company (Abbott)	**3.2**	The publication by Sperzel et al reports pacing performance which has been noted under this section as being a key efficacy outcome.	Thank you for your comment. This study was identified in our update search and has been added to table 2.
38	Consultee 9 Company (Abbott)	**3.5**	Dual chamber leadless pacemakers are in development. For this section to hold true, it would be best if it were to read Current leadless cardiac pacemakers.	Thank you for your comment. IPAC amended section 3.5 as follows: The leadless cardiac pacemakers currently available are only used for right ventricular pacing and are not suitable for people who need sequential pacing or dual-chamber pacing.

"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."