National Institute for Health and Care Excellence

IP1957 Pulsed field ablation for atrial fibrillation

IPAC date: 8th May 2025

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1.	Consultee 3 Boston Scientific	1.1	We support the recommendation that pulsed field ablation be offered as an option to treat atrial fibrillation with standard arrangements given the substantial body of evidence demonstrating its safety and efficacy.	Thank you for your comment. Consultee agrees with main recommendation.
2.	Consultee 5 Clinical	1.1	No comments but I agree with the recommendations	Thank you for your comment. Consultee agrees with main recommendation.
3.	Consultee 6 Patient	1.1	No comments but I agree with the recommendations	Thank you for your comment. Consultee agrees with main recommendation.
4.	Consultee 7 Clinical	1.1	No comments but I agree with the recommendations	Thank you for your comment. Consultee agrees with main recommendation.
5.	Consultee 8 Clinical	1.1	No comments but I agree with the recommendations	Thank you for your comment. Consultee agrees with main recommendation.
6.	Consultee 9 Arrhythmia Alliance	1.1	No comments but I agree with the recommendations	Thank you for your comment. Consultee agrees with main recommendation.
7.	Consultee 1 British Cardiovascular Society	1.1	The British Cardiovascular Society supports the draft recommendations made.	Thank you for your comment. Consultee agrees with main recommendation but notes there

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			However, we would like to draw attention to the fact that the technology (PFA) is not yet well established and outcomes may vary between different versions of the technology.	are different technologies and outcomes may vary between them. Section 3.5 of the draft guidance states 'There are different types of catheter and generators with varying amounts of evidence. The evidence may not be transferable between technologies because of their differences.'
8.	Consultee 1 British Cardiovascular Society	1.1	In addition the requirement for a general anaesthetic may represent an increased resource burden.	Thank you for your comment. The committee considered this comment but did not make any changes to the guidance as this committee does not consider resource impact.
9.	Consultee 1 British Cardiovascular Society	1.1	Ongoing audit and then interval review will be important.	Thank you for your comment. Section 1.2 has been changed to recommend data entry to the NICOR database.
10	Consultee 3 Boston Scientific	1.2 1	To ensure consistency with existing NICE guidance on other forms of cardiac ablation (e.g., IPG427, IPG563) we would suggest that this recommendation is amended to specifically reference the "National Audit of Cardiac Rhythm Management (NACRM) run by the National Institute for Cardiovascular Outcomes Research." rather than referencing registries generically. This is the NHS-mandated registry for centres in England to submit procedural outcomes data to for all cardiac ablation procedures per the NHS England Clinical Commissioning Policy for Catheter ablation for paroxysmal and persistent atrial fibrillation (adults) and understand from	Thank you for your comment. Section 1.2 has been changed to recommend data entry to the NICOR database.

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			the evidence summary document that they have expressed their intention to update the database to incorporate a tag for PFA.	
11	Consultee 2 J&J MedTech	1.2	Healthcare professionals should enter details about everyone having pulsed-field ablation for atrial fibrillation onto a suitable registry. This should include details of patient selection, the technology used and longer-term outcomes. Comment: How long will this be required for? Does the DWG registry process cover this requirement?	Thank you for your comment. Section 1.2 has been changed to recommend data entry to the NICOR database.
12	Consultee 4 Medtronic	1	Medtronic would like to thank NICE for the opportunity to comment on the draft IPG. We would like to publicly reaffirm our ongoing support for the rigorous approach NICE employs in evaluating technologies and procedures, which plays a crucial role in ensuring efficacy and safety for the NHS. However, regarding this particular assessment and its associated process, we feel it is important to address some factual inaccuracies and overlooked evidence.	Thank you for your comment.
13	Consultee 3 Boston Scientific	2.4 The procedure	We would suggest this is amended to read "electric field energy" to be more accurate.	Thank you for your comment. ‘electrical energy’ has been amended to ‘electric field energy’
14	Consultee 3 Boston Scientific	Overview: What the procedure involves	This is inaccurate - please amend to "electric field energy".	Thank you for your comment. ‘electrical energy’ has been amended to ‘electric field energy’
15	Consultee 3 Boston Scientific	Overview: What the procedure involves	This is inaccurate - please amend to "electric field energy".	Thank you for your comment. ‘electrical energy’ has been amended to ‘electric field energy’
16	Consultee 3 Boston Scientific	Unmet need (overview)	This is inaccurate - please amend this to read "electric field".	Thank you for your comment.

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				‘electrical energy’ has been amended to ‘electric field energy’
17	Consultee 3 Boston Scientific	2.3 Unmet need	This is inaccurate - please amend this to read "electric field energy".	Thank you for your comment. ‘electrical energy’ has been amended to ‘electric field energy’
18	Consultee 3 Boston Scientific	2.4 The procedure	We would welcome the inclusion of the word "currently" here to reflect the evolving use of this technology.	Thank you for your comment. Section 2.4 of the draft guidance has been amended to: ‘PFA is currently used most for isolation of abnormal electrical activity transmitted through the pulmonary vein cells at the entrance to the left atrium. But it is also used on other structures such as the left atrial posterior wall and cavo-tricuspid isthmus.’
19	Consultee 3 Boston Scientific	2.4 The procedure	We would welcome the expansion of this comment to better reflect the evolving use of this technology and would suggest it is rephrased as "But it can be used on other structures such as the left atrial posterior wall and Cavo-Tricuspid Isthmus." (https://clinicaltrials.gov/study/NCT05443594?term=advantage%20pfa&rank=1)	Thank you for your comment. Section 2.4 has been amended to: ‘But it is also used on other structures such as the left atrial posterior wall and cavo-tricuspid isthmus.’
20	Consultee 3 Boston Scientific	Overview: What the procedure involves	We would welcome the expansion of this comment to better reflect the evolving use of this technology and would suggest it is rephrased as "But it can be used on other structures such as the left atrial posterior wall and Cavo-Tricuspid Isthmus." (https://clinicaltrials.gov/study/NCT05443594?term=advantage%20pfa&rank=1)	Thank you for your comment. The overview has been amended to: ‘But it is also used on other structures such as the left atrial

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				posterior wall and cavo-tricuspid isthmus.’
21	Consultee 3 Boston Scientific	2.3 Unmet need	We would recommend this is changed to read "targets" rather than "may be able to target". This is a proven concept reported in published studies which demonstrate the tissue specificity of pulsed field ablation (Scheffer et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol. 2014;25(7):997-1011.22; Lavee et al. A novel nonthermal energy source for surgical epicardial atrial ablation: irreversible electro-poration. Heart Surg Forum. 2007;10(2):E162-E167.23; Golberg et al. Nonthermal irreversible electroporation: fundamentals, applications, and challenges. IEEE Trans Biomed Eng.2013;60(3):707-714.)	Thank you for your comment. The committee discussed this comment but agreed not to change the wording for this section. A new committee comment has been added, noting that the committee was informed that PFA targets heart tissue more specifically than thermal ablation. Section 3.10 has been amended to note there may be less damage to surrounding structures.
22	Consultee 3 Boston Scientific	2.3 Unmet need	We would recommend this is changed to read "reduces" rather than "may reduce". The ability for pulsed field ablation to reduce the risk of damage to surrounding structures has been proven for the Farapulse PFA System in published evidence with no reported cases of PV stenosis, oesophageal fistula or persistent phrenic nerve palsy in any publication, including the ADVENT RCT or MANIFEST 17K real-world evidence study of over 17,000 patients.	Thank you for your comment. Please see response to comment 21.
23	Consultee 3 Boston Scientific	Unmet need (overview)	We would recommend this is changed to read "targets" rather than "may be able to target". This is a proven concept reported in published studies which demonstrate the tissue specificity of pulsed field ablation (Scheffer et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vasc Interv Radiol. 2014;25(7):997-1011.22; Lavee et al. A novel nonthermal energy source for surgical epicardial atrial ablation: irreversible electro-poration. Heart Surg Forum. 2007;10(2):E162-E167.23; Golberg et al. Nonthermal	Thank you for your comment. Please see response to comment 21.

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			irreversible electroporation: fundamentals, applications, and challenges. IEEE Trans Biomed Eng.2013;60(3):707-714.)	
24	Consultee 3 Boston Scientific	Unmet need (overview)	We would recommend this is changed to read "reduces" rather than "may reduce". The ability for pulsed field ablation to reduce the risk of damage to surrounding structures has been proven for the Farapulse PFA System in published evidence with no reported cases of PV stenosis, oesophageal fistula or persistent phrenic nerve palsy in any publication, including the ADVENT RCT or MANIFEST 17K real-world evidence study of over 17,000 patients.	Thank you for your comment. Please see response to comment 21.
25	Consultee 3 Boston Scientific	3.1 The evidence	We would recommend that this is qualified with the number of other relevant studies (e.g., "100 other relevant studies"). We believe the current summary here does not sufficiently convey the full body of evidence available for this technology.	Thank you for your comment. Section 3.1 of the draft guidance describes that there was a detailed review of 19 sources. The last sentence states that 'Other relevant literature is in the appendix of the overview.'
26	Consultee 3 Boston Scientific	3.1 The evidence	We would recommend that this is rephrased as "The prioritised evidence" in line with the evidence summary and to clarify this is not the entirety of the evidence base.	Thank you for your comment. Section 3.1 has been amended to: 'The prioritised evidence included 2 systematic reviews and meta-analyses, 1 non-inferiority randomised controlled trial, 4 single-arm trials…'
27	Consultee 3 Boston Scientific	3.5 Committee comments	We would welcome the addition of a qualification statement here to reference the fact that the vast majority of the evidence considered for this guidance is for the Farapulse PFA System.	Thank you for your comment. The committee discussed this comment but agreed not to change this section. Section 3.5 of the guidance notes that there are

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				different systems and further details are given in the overview.
28	Consultee 3 Boston Scientific	Overview: population and studies	We believe it would be helpful to quantify here in the body of the text the number or proportion of total patients treated using the Farawave catheter to better clarify this statement.	Thank you for your comment. The committee discussed this comment but agreed not to make any changes.
29	Consultee 3 Boston Scientific	Overview: procedure technique	As noted above, we would encourage the inclusion of the Mills et al (2024) paper here also. We also believe that - particularly in light of the committee comments made in the draft guidance regarding differences in clinical outcomes being dependent on the catheter used - that it would be beneficial to explicitly quantify the total number of patients treated with the Farawave catheter overall, rather than only by study. We believe this will better reflect the body of evidence available for each catheter at a glance.	Thank you for your comment. Mills (2024) has been added to the key evidence. This section of the overview has been updated with all the new evidence.
30	Consultee 4 Medtronic	Overview: validity	Medtronic would like to inform NICE that the timing of CE approval has significantly influenced the amount of evidence available for Farapulse. Farapulse received its approval 18-24 months earlier than Sphere-9 and PulseSelect, providing it with a head start in accumulating evidence,	Thank you for your comment.
31	Consultee 3 Boston Scientific	Overview: ongoing trials	We would welcome clarification that the Farawave catheter is no longer actively recruiting patients into the MINTAC-related registry as it has been approved for full market release by NHS England.	Thank you for your comment. This section of the overview has been updated.
32	Consultee 4 Medtronic	Overview: ongoing trials	Medtronic would also like to make NICE aware of the PulseSelect PFA Global Registry and PULSED AF Post-Approval Study PulseSelect PFA Global Registry: NCT06393920 PulseSelect™ PFA Global Registry.	Thank you for your comment. The 2 trials have been added to the list of ongoing trials in the overview.

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			https://clinicaltrials.gov/study/NCT06393920?term=pulseselect&rank=1, n=500, global. Estimated completion: 7/1/2027 PULSED AF Post-Approval Study: NCT06578104 PULSED AF Post-Approval Study. https://clinicaltrials.gov/study/NCT06578104?term=pulseselect&rank=2 , n=580, US. Estimated completion: 6/1/2029	
33	Consultee 4 Medtronic	Overview: ongoing trials	Medtronic would also like to make NICE aware of the Affera Global Registry and SPHERE Per-AF Post-Approval Study Affera Global Registry: NCT06026345 Affera Global Registry https://clinicaltrials.gov/study/NCT06026345, Estimated: 540, EU. Estimated completion: 01/07/2028 SPHERE Per-AF Post-Approval Study: NCT06858306 SPHERE Per-AF Post-Approval Study, https://clinicaltrials.gov/study/NCT06858306, Estimated: 200, US. Estimated completion: 10/2030	Thank you for your comment. The 2 trials have been added to the list of ongoing trials in the overview.
34	Consultee 2 J&J MedTech	Overview: p85	Supporting Document • P85 An MHRA safety alert was issued for a series of lot numbers for Varipulse Comment: Field Safety Notice not safety alert. Comment: Please note there are Field Safety notices for other PFA technologies, please can you explain why are these not mentioned in the document? Boston Scientific: 41M402, 41M401, 61M401 FARAWAVE - FARASTAR - FARAPULSE SYSTEM Brand 15 September 2022 Therapy Tissue Ablation MHRA reference: 2022/009/020/611/008	Thank you for your comment. The overview link is to a Field Safety Notice Recall. The paragraph heading ‘MHRA safety alert’ has been changed to ‘MHRA Field Safety Notice Recall’ This was included in the overview because it states potential impacts on patient safety whereas the other MHRA field safety notice is a clarification on indicated population which is already acknowledged in the updated company IFU.

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35	Consultee 3 Boston Scientific	Lay description	This is factually incorrect as electricity is not directly applied. We suggest this is amended to the following: "In this procedure, short bursts or "pulses" of electric fields (pulsed field) are used to preferentially destroy (ablate) the heart cells that are causing irregular beats."	Thank you for your comment. The lay description has been amended to: 'In this procedure, short bursts or pulses of electric fields (pulsed-field) are used to specifically destroy the heart cells (ablation) that are causing irregular beats.'
36	Consultee 3 Boston Scientific	Overview: procedure technique	We would welcome the clarification that the anaesthetic approach is often dependent on local country regulations where the study has been conducted.	Thank you for your comment. The overview currently states 'In the NHS, the procedure is usually done under GA but deep sedation is often used in other countries.' In 'procedure technique', the overview states 'Some studies only used GA, whilst others used a mixture of GA and conscious or deep sedation. Schmidt (2022) and the inspIRE sub study (Grimaldi 2023) both used deep sedation only.' The committee discussed this comment but agreed not to make any changes.
37	Consultee 4 Medtronic	Overview: procedure technique	Amend text to include deep sedation	Thank you for your comment. The overview currently states 'In the NHS, the procedure is usually done under GA but deep sedation is often used in other countries.'

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				In 'procedure technique', the overview states 'Some studies only used GA, whilst others used a mixture of GA and conscious or deep sedation. Schmidt (2022) and the inspIRE sub study (Grimaldi 2023) both used deep sedation only.' The committee discussed this comment but agreed not to make any changes.
38	Consultee 3 Boston Scientific	3.1 The evidence	We would like to highlight that the review undertaken for this draft guidance has not included a recently published UK multi-centre experience including 1,034 PFA procedures using the Farawave PFA catheter. Given the significance of this publication and relevance to this assessment, we would encourage it's inclusion here. (Mills MT, Trivedi S, Lovell MJ et al. Pulsed-field ablation of atrial fibrillation with a pentaspline catheter across National Health Service England centres. Open Heart. 2024 Dec 18;11(2):e003094. doi: 10.1136/openhrt-2024-003094. PMID: 39694575; PMCID: PMC11667399.)	Thank you for your comment. Mills (2024) has been added to the key evidence.
39	Consultee 3 Boston Scientific	Overview: population and studies	We would like to highlight that the review undertaken for this draft guidance has not included a recently published UK multi-centre experience including 1,034 PFA procedures using the Farawave PFA catheter. Given the significance of this publication and relevance to this assessment, we would encourage it's inclusion here. (Mills MT, Trivedi S, Lovell MJ et al. Pulsed-field ablation of atrial fibrillation with a pentaspline catheter across National Health Service England centres. Open Heart. 2024 Dec 18;11(2):e003094. doi: 10.1136/openhrt-2024-003094. PMID: 39694575; PMCID: PMC11667399.)	Thank you for your comment. Mills (2024) has been added to the key evidence.

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40	Consultee 3 Boston Scientific	Overview: ongoing trials	We believe it would be beneficial to reference here that the registry data collected on the Farawave catheter has now been published (Mills MT, Trivedi S, Lovell MJ et al. Pulsed-field ablation of atrial fibrillation with a pentaspline catheter across National Health Service England centres. Open Heart. 2024 Dec 18;11(2):e003094. doi: 10.1136/openhrt-2024-003094. PMID: 39694575; PMCID: PMC11667399.)	Thank you for your comment. Mills (2024) has been added to the key evidence.
41	Consultee 4 Medtronic	Overview: evidence summary	Medtronic would like to make NICE aware that this study is completed, and the results have been published in August 2024 by Anter et al. Link to the study https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
42	Consultee 4 Medtronic	Overview: population and studies	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) in the document, as it is currently missing from the evidence regarding Affera Sphere-9. This prospective RCT of 420 randomized people treated across 20 centres in the US and EU, conducted by Anter et al., was published in August 2024 and evaluated the safety and efficacy of Affera Sphere-9 with dual energy radiofrequency and pulse field vs. the conventional contact force sensing radiofrequency. You can access the study results via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
43	Consultee 4 Medtronic	Overview: population and studies	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) in the document, as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. You can access the study results via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
44	Consultee 4 Medtronic	Overview: procedure technique	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was	Thank you for your comment. Anter (2024) has been added to the key evidence.

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			published in August 2024. You can access the study results via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	
45	Consultee 4 Medtronic	Overview: procedure technique	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
46	Consultee 4 Medtronic	Overview: efficacy	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/. Some suggested verbiage “In SPHERE Per-AF (Sphere-9), the interventional, prospective, randomized control trial of 420 randomized subjects across 20 centres (Anter 2024), treatment success was defined as inability to isolate all targeted pulmonary veins during the index procedure, any left atrial ablation done with non-assigned study device during the index procedure, any repeat ablation or surgery for AF/AT/AFL recurrence after the index procedure, direct current cardioversion for AF/AT/AFL recurrence after the 90 day blanking period, documented AF/AT/AFL recurrence after the 90 day blanking period, initiation of a new class I/III AAD during after the 90 day blanking period or class I/III AAD increase from historic maximum ineffective dose. A detailed listing of the primary effectiveness endpoint events is listed in the publication and included in extended data table to the publication. The primary effectiveness endpoint success rate was 73.8% for the investigational arm and 65.8% for the control arm. The observed difference in primary effectiveness success was 8.0% in favor of the investigational arm (95%	Thank you for your comment. Anter (2024) has been added to the key evidence.

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			confidence interval (CI): −0.9% to 16.8%), meeting the criteria for non-inferiority (P < 0.0001). The 1-year Kaplan–Meier estimates were 73.5% for the investigational arm and 65.2% for the control arm.”	
47	Consultee 4 Medtronic	Overview: efficacy	Medtronic requests that NICE remove the current statement and instead include the Affera SPHERE Per-AF Randomized Controlled Trial (RCT) (NCT05120193). This RCT compares the dual energy radiofrequency (RFA) and pulsed field ablation (PFA) using Sphere-9 with conventional contact force sensing thermal ablation using radiofrequency. Conducted by Anter et al., the study was published in August 2024. For more details, please refer to the study results: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
48	Consultee 4 Medtronic	Overview: efficacy	The Sphere-9 First-In-Human and Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) both included additional lesions.	Thank you for your comment. Anter (2024) has been added to the key evidence.
49	Consultee 4 Medtronic	Overview: efficacy	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. The study reported improved quality of life after ablation in both the investigational (Sphere-9) and control (convention contact force sensing radiofrequency) groups. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
50	Consultee 4 Medtronic	Overview: efficacy	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. The study reported a 4.8% (10 of 210 Sphere-9 patients) repeat ablation or surgery for AF/AT/AFL recurrence after the index procedure. The control arm (conventional RF)	Thank you for your comment. Anter (2024) has been added to the key evidence.

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			reported an 8.4% (17 of 202 patients) repeat ablation or surgery for AF/AT/AFL recurrence after the index procedure. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	
51	Consultee 4 Medtronic	Overview: efficacy	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. The study reported 95.8% of patients receiving additional linear ablation beyond PVI. You can access the study results via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
52	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. There were no Sphere-9 reported myocardial infarction events observed in the study, there was 1 report of myocardial infarction with the conventional contact force sensing radiofrequency catheter. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
53	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. Both treatment arms demonstrated a low rate of primary safety events (1.4% for the investigational arm and 1.0% for the control arm) with no evidence of major complications, such as stroke, tamponade, atrio-esophageal fistula or permanent phrenic nerve paralysis. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.

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54	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. There were no Sphere-9 reported evidence of PV stenosis in the study. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
55	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) also reported no heart rate change or ST segment changes (0% [0 of 212 Sphere-9 patients]). This RCT, conducted by Anter et al., was published in August 2024. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
56	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
57	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. The study reported 8.1% (3 of 37 Sphere-9 patients) had acute ischemia with FLAIR hyperintensity and 8.1% (3 of 37 Sphere-9 patients) had acute ischemia without FLAIR hyperintensity. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
58	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. The study reported there were no (0% [0 of	Thank you for your comment. Anter (2024) has been added to the key evidence.

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			212 patients]) pericarditis events with Sphere-9, there were 3 (1.4% [3 of 208 patients]) reported pericarditis events with the conventional contact force sensing radiofrequency catheter. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	
59	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) where 0% (0 of 212 Sphere-9 patients) had major vascular access complications reported. This RCT, conducted by Anter et al., was published in August 2024. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
60	Consultee 4 Medtronic	Overview: safety	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. There were no reported thromboembolic events observed in the study. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
61	Consultee 4 Medtronic	Overview: validity	Medtronic requests that NICE include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024 and evaluated the safety and efficacy of Affera Sphere-9 with dual energy radiofrequency and pulse field vs. the conventional contact force sensing radiofrequency. You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
62	Consultee 4 Medtronic	Overview: evidence summary	We kindly ask NICE to include the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193), as it is currently missing from the evidence regarding Affera Sphere-9. This RCT, conducted by Anter et al., was published in August 2024. The Sphere-9 system was superior to the conventional radiofrequency system in measures of	Thank you for your comment. Anter (2024) has been added to the key evidence.

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			procedural efficiency, with shorter procedural duration (shorter skin-to-skin procedural time [100.9 ± 30.8 min versus 126.1 ± 49.2 min; difference: −25.1 min, 95% CI −33.0 to −17.3, P < 0.0001]). You can access the study via this link: https://pubmed.ncbi.nlm.nih.gov/38760584/	
63	Consultee 4 Medtronic	Overview: evidence summary	We would like to highlight that the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) also had no reports of tamponade or perforation (0% [0 of 212 Sphere-9 patients]). Link to paper: https://pubmed.ncbi.nlm.nih.gov/38760584/	Thank you for your comment. Anter (2024) has been added to the key evidence.
64	Consultee 4 Medtronic	Overview: population and studies	In the primary paper, the study is described as a paired single-arm trial as there were two cohorts evaluated (Paroxysmal AF and Persistent AF)	Thank you for your comment. Wording in the overview has been amended to: 'Prioritised evidence for the PulseSelect catheter (Medtronic) was from an international prospective paired single-arm trial of 300 people across 41 centres (PULSED AF, Verma 2023a, Verma 2023b).'
65	Consultee 4 Medtronic	Overview: table 2	Regarding the statement "This study compared effects between a combined RFA and PFA approach with a PFA only approach". The design of the study was not to compare RFA+PFA vs. PFA. The study was designed to assess safety and performance of Sphere-9 in a mixed group of PAF and PersAF patients. Please update language to correct.	Thank you for your comment. The description for Reddy (2023b) under 'intervention' in table 2 has been amended.
66	Consultee 4 Medtronic	Overview: table 2	Medtronic requests NICE to amend the wording to the following: • In the PAF group: treatment success was observed in 100 of 150 people (66.7%). 1-year Kaplan-Meier estimate 66.2% (95%CI 57.9 to 73.2%).	Thank you for your comment. The wording for the efficacy outcomes in the PULSED AF trial (Verma 2023a) has been amended.

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			• In the PersAF group: treatment success was observed in 83 of 150 people (55.3%). 1-year Kaplan-Meier estimate 55.1% (95% CI 46.7 to 62.7%).	
67	Consultee 4 Medtronic	Overview: efficacy	The current wording is somewhat confusing. Technically, the primary effectiveness endpoint is defined as acute procedural failure, atrial arrhythmia (AA) recurrence, or antiarrhythmic drug (AAD) escalation. The reported values indicate treatment success or the absence of a primary efficacy endpoint event. Medtronic requests that NICE amend the wording to the following: "In the PAF group, treatment success was observed in 67% of people met the primary effectiveness endpoint and the 1-year Kaplan-Meier estimate was 66% (95%CI 58 to 73%). In the PersAF group, treatment success was observed in 55% of people met the primary effectiveness endpoint and the 1-year Kaplan-Meier estimate was 55% (95% CI 47 to 63%)."	Thank you for your comment. The description of efficacy outcomes for the PULSED AF trial (Verma 2023a) has been amended in the efficacy summary section of the overview to be consistent with the change in table 2.
68	Consultee 4 Medtronic	Overview: population and studies	Medtronic requests NICE to remove the mention of symptomatic as this analysis included all atrial arrhythmia recurrence, not just symptomatic.	Thank you for your comment. The paragraph in the efficacy column for the PULSED AF trial has been amended to: Verma (2023b) reported further detail on atrial arrhythmia burden after the blanking period. Burden definition was calculated as the higher of 1) percentage of atrial arrhythmia on total Holter time; or (2) percentage of weeks with 1 or more transtelephonic monitoring with atrial arrhythmia recurrence, out of all weeks with 1 or more

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				transtelephonic monitoring transmission'
69	Consultee 4 Medtronic	Overview: population and studies	This section and comment are misleading, the primary safety endpoint was the composite occurrence of study device-related serious AEs within 7 days of the procedure (unless otherwise specified): including death, myocardial infarction, PV stenosis (through study exit), persistent diaphragmatic paralysis, atrioesophageal fistula (through study exit), stroke/transient ischemic attack/thromboembolism, cardiac tamponade or perforation, pneumothorax, major vascular complications, pulmonary oedema, hospitalization (initial and prolonged), or heart block. The primary safety event rate was 0.6% (1 of 178 people). The 1 primary safety event occurred in a patient who received RF and PF ablation at the index procedure. 20 days post procedure, patient was hospitalized for inflammatory pericardial effusion managed with anti-inflammatory medication. We would also like to highlight that the study reported results of 122 patients who underwent ICE and invasive remapping with no reports of PV stenosis, 77 patients with cardiac computed tomography scans with no reports of PV stenosis and 124 patients who underwent post-procedure esophagogastroduodenoscopy with no reports of atrioesophageal fistula.	Thank you for your comment. The wording has been amended.
70	Consultee 4 Medtronic	Overview: efficacy	We kindly ask NICE to amend this text regarding HRQoL from Verma 2023b to the following: "Additional analyses in Verma (2023b) found that most benefit in people with PAF was seen if they had no atrial arrhythmia burden at 12 months. Clinically relevant improvements in AF-specific quality of life were driven by people with less than 10% atrial arrhythmia burden in the PAF cohort. Patients in the PersAF cohort had clinically relevant improvements in AF-specific quality of life regardless of atrial arrhythmia burden."	Thank you for your comment. The wording has been amended as suggested.

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71	Consultee 4 Medtronic	Overview: safety	Medtronic requests NICE to further clarify that there were 124 patients in the Sphere-9 EU trial that had post procedure oesophagogastroduodenoscopy and that only 3 of those patients with mild oesophageal lesions. Of which all 3 patients were asymptomatic minor mucosal thermal injury in the RF/PF cohort. Medtronic also requests that the “around 2.3 degrees Celsius” be updated to read “around 2-3 degrees Celsius.” Medtronic also requests NICE to further clarify and reference the Affera SPHERE Per-AF Randomised Controlled Trial (RCT) (NCT05120193) where 63 (29.7%) subjects had oesophageal temperature probe with no reports of AE fistula or other fistula injury.	Thank you for your comment. The description of the Sphere-9 trial outcomes under ‘Oesophageal lesions and injury’ has been changed to: ‘In the publication that combined evidence from 2 prospective single-arm trials done with the Sphere-9 catheter (178 people across 3 EU centres; Reddy 2023b) low level heating (around 2 to 3 degrees Celsius) was seen when PFA was done along the left atrial posterior wall. Post-procedure oesophagogastroduodenoscopy was done in 124 people, which showed 3 instances (2%) of asymptomatic minor mucosal thermal injury, all of which were in the subgroup of 36 people who had RFA and PFA. There were no injuries in the PFA only group.’ Anter (2024) has been added to the key evidence.
72	Consultee 4 Medtronic	Overview: validity	While the rate of cardiac tamponade was higher in the PFA compared to the thermal ablation group in two recent meta-analyses of randomised and non-randomised comparative studies, the overall incidence of cardiac tamponade reported with PFA (1%) was well within the range previously reported with thermal ablation in prospective registries (0.5-1.3%) (Hindricks, 2020). Many of the included publications in the	Thank you for your comment. Wording in the overview has been changed to clarify that the overall

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			referenced meta analyses report outcomes with initial use of PFA in relatively small patient cohorts. Importantly, operator experience is a critical factor associated with complication rates after catheter ablation for atrial fibrillation (Van Gelder, 2024). Indeed, in the largest dataset evaluating safety with commercial use of pulsed field ablation to date (n=17,642), the rate of pericardial tamponade was 0.36%. A learning curve analysis found a strong trend for a reduction in the rate of cardiac tamponade between the first 1,758 vs. subsequent 7,878 procedures at 24 centres with early commercial adoption of PFA (rate of pericardial tamponade: 0.97% versus 0.43%, P = 0.093) (Ekanem, 2024). In a root cause analysis of cardiac tamponade in the first 1,758 patients treated, 4/17 events (24%) were attributed to the extra-stiff straight-tip guidewire used during catheter positioning resulting in perforation of the LAA or PVs (Ekanem, 2022). This cause is 1) system-specific, 2) unrelated to PFA energy delivery, and 3) avoidable using a J-tip guidewire. Additionally, the rate of cardiac tamponade observed in CE Mark and IDE trials evaluating PFA systems for the treatment of AF has been low (ranging from 0% to 1.1%) (Anter et al., 2024, Duytschaever et al., 2023, Reddy et al., 2023, Reddy et al., 2024, Verma et al., 2023) - Duytschaever M, De Potter T, Grimaldi M, Anic A, Vijgen J, Neuzil P, et al. inspIRE Trial Investigators. Paroxysmal Atrial Fibrillation Ablation Using a Novel Variable-Loop Biphasic Pulsed Field Ablation Catheter Integrated With a 3-Dimensional Mapping System: 1-Year Outcomes of the Multicenter inspIRE Study. Circ Arrhythm Electrophysiol. 2023 Mar;16(3):e011780. doi: 10.1161/CIRCEP.122.011780. Epub 2023 Feb 3.	rate of cardiac tamponade ranged from 0 to 1%. Anter (2024) has been added to the key evidence.

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			- Ekanem, E. et al. (2022) 'Multi-national survey on the methods, efficacy, and safety on the post-approval clinical use of pulsed field ablation (MANIFEST-PF),' EP Europace, 24(8), pp. 1256–1266. https://doi.org/10.1093/europace/euac050. - Ekanem, E. et al. (2024) 'Safety of pulsed field ablation in more than 17,000 patients with atrial fibrillation in the MANIFEST-17K study,' Nature Medicine, 30(7), pp. 2020–2029. https://doi.org/10.1038/s41591-024-03114-3. - Hindricks, G. et al. (2020) '2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS),' European Heart Journal, 42(5), pp. 373–498. https://doi.org/10.1093/eurheartj/ehaa612. - Reddy VY, Peichl P, Anter E, Rackauskas G, Petru J, Funasako M, et al. A Focal Ablation Catheter Toggling Between Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation. JACC Clin Electrophysiol. 2023 Aug;9(8 Pt 3):1786-1801. doi: 10.1016/j.jacep.2023.04.002. Epub 2023 Apr 16. - Reddy VY, Calkins H, Mansour M, Wazni O, Di Biase L, Bahu M et al. AdmIRE Trial Investigators. Pulsed Field Ablation to Treat Paroxysmal Atrial Fibrillation: Safety and Effectiveness in the AdmIRE Pivotal Trial. Circulation. 2024 Oct 8;150(15):1174-1186. doi: 10.1161/CIRCULATIONAHA.124.070333. Epub 2024 Sep 11. - Van Gelder, I.C. et al. (2024) '2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS),' European Heart Journal [Preprint]. https://doi.org/10.1093/eurheartj/ehae176. - Verma A, Haines DE, Boersma LV, Sood N, Natale A, Marchlinski FE, et al. Pulsed Field Ablation for the Treatment	

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			of Atrial Fibrillation: PULSED AF Pivotal Trial. Circulation. 2023 May 9;147(19):1422-1432. doi: 10.1161/CIRCULATIONAHA.123.063988. Epub 2023 Mar 6.	

"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."