NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 27 February 2020

THEME: Clinical significance of additional cases of AF detected by implantable cardiac monitors

Comment number	Name and organisation	Section number	Comment	NICE response
1	NHS Professional	General	General Comments: 1) Many consider AF as stroke risk association, not necessarily a direct causative risk of stroke 2) Most people over 50 years have a few runs of AF if you monitor them for long enough - so what? 3) We need STRONG evidence that anticoagulating in those with rare AF is a) Safe b) shows ANY benefit overall in reducing mortality & ill health (inc. stroke) Thanks	Thank you for your comment which the committee considered. The committee noted that while it was likely that using Reveal implantable cardiac monitors in the NHS would result in more atrial fibrillation being detected, there was uncertainty about the extent that subsequent treatment decisions would reduce the number of further strokes or TIAs that would occur (see section 4.5 of the diagnostics guidance document). But the committee agreed that, in the absence of long-term data on this, the external assessment group's (EAG's) approach of linking evidence on the extent of atrial fibrillation detection by an implantable cardiac monitor, the impact of diagnosis on treatment choice (switching from antiplatelet agents to anticoagulants on atrial fibrillation diagnosis), and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model, was suitable for decision making (see section 4.8 of the diagnostics guidance document). The EAG estimated the impact of switching to anticoagulants after

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				atrial fibrillation is diagnosed (compared to antiplatelet therapy) on the likelihood of having clinical events such as stroke and TIA by using a recent meta-analysis that incorporated data from numerous studies identified by systematic review. The EAG adjusted the size of impact of anticoagulant on clinical events to represent a population who had already had a stroke and who had paroxysmal atrial fibrillation as had been done in Welton et al. (2017) – as referenced in the diagnostic assessment report. While noting the uncertainty in cost effectiveness results, the committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained. Therefore, the committee concluded that Reveal LINQ is likely to be a cost-effective use of NHS resources (see section 4.16 of the diagnostics guidance document). Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a

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				systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.
2	NHS Professional	General	It is very surprising to me that the recommendations on cost effectiveness are based very largely on modelling rather than requiring and waiting for adequate real world data. This approach would not be taken by NICE in assessing a drug for approval and there is no need in this case to do this for a device based on such limited evidence and what appears to be wishful thinking There seems to be little consideration in the report of the counter arguments and I believe a more rigorous health economic evaluation would conclude that there is not enough evidence to make a recommendation for use at this stage. There is the opportunity for NICE to influence the gathering of better quality evidence and this is being wasted.	Thank you for your comment which the committee considered. The NICE diagnostics assessment programme manual states that if there are no end-to-end studies available for a diagnostic technology, then different types of evidence are collected and a linked evidence approach can be taken (section 13.2). That is, if there is no direct evidence on how using a test impacts on clinical outcomes (for example, stroke recurrence) economic modelling can be used to estimate the impact by linking evidence on how using the test will increase detection of a condition, how this would impact on treatment decisions and how this would ultimately impact on clinical outcomes. The committee noted that while it was likely that using Reveal implantable cardiac monitors in the NHS would result in more atrial fibrillation being detected, there was uncertainty about the extent that subsequent treatment decisions would reduce the number of further strokes or

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				TIAs that would occur (see section 4.5 of the diagnostics guidance document). But the committee agreed that, in the absence of long-term data on this, the external assessment group's (EAG's) approach of linking evidence on the extent of atrial fibrillation detection by an implantable cardiac monitor, the impact of diagnosis on treatment choice (switching from antiplatelet agents to anticoagulants on atrial fibrillation diagnosis), and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model, was suitable for decision making (see section 4.8 of the diagnostics guidance document). The EAG estimated the impact of switching to anticoagulants after atrial fibrillation is diagnosed (compared to antiplatelet therapy) on the likelihood of having clinical events such as stroke and TIA by using a recent meta-analysis that incorporated data from numerous studies identified by systematic review. The EAG adjusted the size of impact of anticoagulant on clinical events to represent a population who had already had a stroke and who had paroxysmal atrial fibrillation as had been done in Welton

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				et al. (2017) – as referenced in the diagnostic assessment report. While noting the uncertainty in cost effectiveness results, the committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained. Therefore, the committee concluded that Reveal LINQ is likely to be a cost-effective use of NHS resources (see section 4.16 of the diagnostics guidance document). The EAG commented that it considered and utilised data from all available clinical evidence in its report and its cost-effectiveness analysis. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.
3	NHS Professional	General	We are astonished that the committee has elected to come up with these guidelines which are based on AF detection rather than the prevention of another stroke which is clearly the most relevant clinically. We	Thank you for your comment which the committee considered.

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			are concerned that the guidelines are solely based on implanting, rather than defining a clear population to implant in, a clear definition of AF, and how to manage arrhythmias detected by the device. We know that we will detect more AF with ILRs, but there is no clear association with this detected AF and re-stroke (Crystal AF did not show any significant difference in re-stroke). Crystal AF shows that we detect more AF with these devices, and for this reason, implanting ILRs is reasonable, however, there is an assumption that implanting ILRs will lead to more anticoagulation and this will prevent re-stroke. This evidence is lacking, and without this clear evidence, the clinical role of these devices is questionable. Moreover, there is good data showing that the link between an episode of AF and stroke is not clear cut (device data). The document deals with cryptogenic stroke. Data from Crystal AF was heavily relied on. If the baseline	The diagnostics guidance has been amended to specify that Reveal LINQ is recommended for use for people who have had cryptogenic stroke and for whom non-invasive electrocardiogram (ECG) monitoring has been done, and a cardiac arrhythmic cause of stroke is still suspected (see section 1.1 of the diagnostics guidance document). The NICE clinical guidance on atrial fibrillation management recommends offering anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account. Clinical experts commented that because everyone who has had a cryptogenic stroke or TIA has a CHA_2DS_2-VASc score of at least 2, if an episode of atrial fibrillation of at least 30 seconds is seen in these patients they would routinely be offered anticoagulants. Ultimately it will be a clinician who decides if, on the basis of an episode of atrial fibrillation detected by the monitor, this is sufficient for anticoagulants to be offered. The committee noted that while it was likely that using Reveal implantable cardiac monitors in the NHS would result in more atrial fibrillation being detected, there was

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			characteristics of the patients are studied, 60% had hypertension, 20% had diabetes and the majority were in their 60s. These are clear risk factors for stroke and AF. With so many of these strong traditional risk factors present, how can we truly call this group cryptogenic? Further, the definition of cryptogenic was mainly based on carotid scans and echos (cerebral angios were not routinely performed). How do these clearly exclude the presence of atherosclerosis (e.g. in the aorta)? How many patients in Crystal AF had basal ganglial infarcts which are generally not a result of embolism? No guidance is provided on what constitutes the minimum irregularly irregular rate we call AF. The definition from the trial was >30s. Currently the role of AHREs in stroke and their treatment is highly debatable. Guidance on whom to anti coagulate is therefore clearly needed. Without this, implantation is pointless. Further in Crystal AF the use of anticoagulation in patients with device detected arrhythmia did not reduce the risk of re-stroke.	uncertainty about the extent that subsequent treatment decisions would reduce the number of further strokes or TIAs that would occur (see section 4.5 of the diagnostics guidance document). But the committee agreed that, in the absence of long-term data on this, the external assessment group's (EAG's) approach of linking evidence on the extent of atrial fibrillation detection by an implantable cardiac monitor, the impact of diagnosis on treatment choice (switching from antiplatelet agents to anticoagulants on atrial fibrillation diagnosis), and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model, was suitable for decision making (see section 4.8 of the diagnostics guidance document). The EAG estimated the impact of switching to anticoagulants after atrial fibrillation is diagnosed (compared to antiplatelet therapy) on the likelihood of having clinical events such as stroke and TIA by using a recent meta-analysis that incorporated data from numerous studies identified by systematic review. The EAG adjusted the size of impact of anticoagulant on clinical events to represent a population who had already had a stroke and who had

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			We would strongly recommend the committee review their recommendations. Loop recorders probably have a niche role in the management of patients with TRUE cryptogenic stroke. This guidance is likely to greatly increase the use of these devices which are expensive, increase the work load of the cardiac physiology department (not included in the cost model) and increase referrals to cardiology (noise, broad complex tachycardia). In the absence of clear evidence that implantation of these devices prevents re-stroke, it is important we get a better evidence base prior to implementation.	paroxysmal atrial fibrillation as had been done in Welton et al. (2017) – as referenced in the diagnostic assessment report. While noting the uncertainty in cost effectiveness results, the committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained. Therefore, the committee concluded that Reveal LINQ is likely to be a cost-effective use of NHS resources (see section 4.16 of the diagnostics guidance document). The committee noted the investigations that had to be done to identify a potential cause of stroke or TIA before a person was enrolled in CRYSTAL-AF (that is, for a stroke or TIA to be classed as cryptogenic). The committee concluded that the population in the CRYSTAL AF study broadly represented people with cryptogenic stroke or TIA who would have an implantable cardiac monitor fitted in NHS practice. The EAG also commented that, based on expert advice, they considered that the definition of cryptogenic stroke used in CRYSTAL-AF was reasonable. But it acknowledged

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				that not all patients may have received computed tomography angiography or magnetic resonance angiography, and that a breakdown of numbers of patients receiving each type of imaging prior to randomisation was not provided in the study publication. The recommendation for use of Reveal LINQ has been amended to clarify that it should only be used if a clinician considers that a stroke or TIA is truly cryptogenic, non-invasive ECG monitoring has been done, and a cardiac arrhythmic cause of stroke is still suspected (see section 1.1 of the diagnostics guidance document). The base-case model did not include the cost of interpreting alerts produced by Reveal LINQ because of a lack of data on the number of alerts produced by the device**.** Including estimated costs for reviewing alerts in the economic model would increase the base case ICER for Reveal LINQ**.** The EAG did 2 scenario analyses that included the costs of an optional triage service for alerts offered by Medtronic for Reveal LINQ. This increased the ICER by about £2,600 to £3,800 per QALY gained,

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				depending on the cost option used. The clinical experts said that the costs used (£187 per patient per year or £374 per patient) are likely to be a realistic estimate and could be considered a reasonable proxy for the costs of triaging alerts in the NHS (see section 4.12 of the diagnostic guidance document). Taking this into account, the committee concluded that while this would increase the base-case ICER, it was unlikely to increase to over £20,000 per QALY gained. The committee concluded that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained (see section 4.15 of the diagnostic guidance document). Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.
4	British Association of Stroke Physicians		5) One might also need to recognise that there is limited evidence about the clinical implications of very brief episodes of AF detected with the REVEAL device (or any other device for prolonged cardiac monitoring) – more than 1/3 of the AF detected in the	Thank you for your comment which the committee considered. The EAG estimated the impact of switching to anticoagulants after atrial fibrillation is diagnosed

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			Crystal AF trial were <2min for example. Hence some of the cost-effective analyses might be difficult to interpret and this is certainly an area that requires further research.	(compared to antiplatelet therapy) on the likelihood of having clinical events such as stroke and TIA by using a recent meta-analysis that incorporated data from numerous studies identified by systematic review. The EAG adjusted the size of impact of anticoagulant on clinical events to represent a population who had already had a stroke and who had paroxysmal atrial fibrillation as had been done in Welton et al. (2017) – as referenced in the diagnostic assessment report. While noting the uncertainty in cost effectiveness results, the committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained. Therefore, the committee concluded that Reveal LINQ is likely to be a cost-effective use of NHS resources (see section 4.16 of the diagnostics guidance document). Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.

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5	British Association of Stroke Physicians		10) One might also need to recognise that there is limited evidence about the clinical implications of very brief episodes of AF detected with the REVEAL device (or any other device for prolonged cardiac monitoring) – more than 1/3 of the AF detected in the Crystal AF trial were <2min for example. The efficacy of anticoagulation in this population in uncertain, and is indeed the subject of ongoing trials. Hence some of the cost-effective analyses might be difficult to interpret and this is certainly an area that requires further research.	Thank you for your comment which the committee considered. The EAG estimated the impact of switching to anticoagulants after atrial fibrillation is diagnosed (compared to antiplatelet therapy) on the likelihood of having clinical events such as stroke and TIA by using a recent meta-analysis that incorporated data from numerous studies identified by systematic review. The EAG adjusted the size of impact of anticoagulant on clinical events to represent a population who had already had a stroke and who had paroxysmal atrial fibrillation as had been done in Welton et al. (2017) – as referenced in the diagnostic assessment report. While noting the uncertainty in cost effectiveness results, the committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained. Therefore, the committee concluded that Reveal LINQ is likely to be a cost-effective use of NHS resources (see section 4.16 of the diagnostics guidance document).

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				Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.
6	British Association of Stroke Physicians		12) There is no mention of the ESUS studies which examined the efficacy of NOACS in the patients with cryptogenic stroke. In these studies, there was no benefit of anticoagulation, suggesting that the burden of unrecognised, important AF may be lower than previously anticipated.	Thank you for your comment which the committee considered. For the effect of anticoagulants on clinical outcomes (compared to antiplatelet agents) used in the model, the EAG used a systematic review and meta-analysis done by Sterne et al. (2017), as well as a further study by Welton et al. (2017) which built on this study. Sterne et al. identified 23 RCTs for inclusion in the review. The committee considered that this approach, and this data source, was suitable for decision-making. As no specific studies are mentioned in the stakeholder's comment it is not possible to comment on whether they were included in the Sterne et al. meta-analysis. Sterne JA, Bodalia PN, Bryden PA, Davies PA, Lopez-Lopez JA, Okoli GN, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network

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				meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2017;21(9):1-386. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.
7	British Association of Stroke Physicians		- CRYSTAL-AF was not powered to detect a difference between groups in stroke and TIA incidence, nor clinical outcome, therefore a number of assumptions have to be incorporated in the model in order to estimate clinical and cost effectiveness. This is acknowledged in the consultation document.	Thank you for your comment which the committee considered.
8	British Cardiovascular Society		The British Cardiovascular Society and British Heart Rhythm Society have reviewed the draft guidelines "Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke". We note in particular the recommendation that the Reveal LINQ device should be offered routinely to patients (after	Thank you for your comment which the committee considered. The committee noted that while it was likely that using Reveal implantable cardiac monitors in the NHS would result in more atrial fibrillation being detected, there was uncertainty about the extent that subsequent treatment decisions would reduce the number of further strokes or TIAs that would occur (see section 4.5 of the diagnostics guidance document). But the committee agreed that, in

			ECG testing for AF and when no alternative cause for stroke is evident). Our societies do have concerns about this recommendation. Specifically, we feel that due to the limited evidence base (which is acknowledged in the draft guideline) there is insufficient evidence that a routine policy of implanting these devices will lead to a definite reduction of stroke from a cost effective perspective. We acknowledge that the device will increase the detection of atrial fibrillation and this is likely to result in increased use of anticoagulation in these patients. However, this strategy has not been tested in a suitably powered outcome study. We also would like to emphasise that this is an invasive intervention with a risk of harm. There is also the anxiety that patients suffer from both device implantation and from living with the impact of an internalised heart rhythm recording device.	the absence of long-term data on this, the external assessment group's (EAG's) approach of linking evidence on the extent of atrial fibrillation detection by an implantable cardiac monitor, the impact of diagnosis on treatment choice (switching from antiplatelet agents to anticoagulants on atrial fibrillation diagnosis), and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model, was suitable for decision making (see section 4.8 of the diagnostics guidance document). The EAG estimated the impact of switching to anticoagulants after atrial fibrillation is diagnosed (compared to antiplatelet therapy) on the likelihood of having clinical events such as stroke and TIA by using a recent meta-analysis that incorporated data from numerous studies identified by systematic review. The EAG adjusted the size of impact of anticoagulant on clinical events to represent a population who had already had a stroke and who had paroxysmal atrial fibrillation as had been done in Welton et al. (2017) – as referenced in the diagnostic assessment report. While noting the uncertainty in cost effectiveness results, the committee considered that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per

			The benefit of the detection of brief asymptomatic arrhythmias is also unclear and there is also the risk of false positives. [*Part of comment moved to another theme section*] There are also the risks of anticoagulation in patients with less clear benefit than in conventional indications for anti-coagulation.	QALY gained. Therefore, the committee concluded that Reveal LINQ is likely to be a cost-effective use of NHS resources (see section 4.16 of the diagnostics guidance document). Recommendation 1.1 has been amended to clarify that Reveal LINQ is an option for use after cryptogenic stroke. As noted in the stakeholder's comment, this needs an invasive procedure to implant so would need to be discussed with a patient, including a discussion of the potential risks and implications of implanting the device. The committee noted that because the results from the device would be reviewed by a trained healthcare professional the risk of a false positive diagnosis of atrial fibrillation is very low. The committee noted that the base-case model did not include the cost of interpreting alerts produced by Reveal LINQ because of a lack of data on the number of alerts produced by the device. Including estimated costs for reviewing alerts in the economic model would increase the base case ICER for Reveal LINQ**.** The EAG did 2 scenario analyses that included the costs of an optional triage service for alerts offered by Medtronic for Reveal LINQ. This increased the ICER by about £2,600 to £3,800 per QALY gained,

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				depending on the cost option used. The clinical experts said that the costs used (£187 per patient per year or £374 per patient) are likely to be a realistic estimate and could be considered a reasonable proxy for the costs of triaging alerts in the NHS (see section 4.12 of the diagnostic guidance document). Taking this into account, the committee concluded that while this would increase the base-case ICER, it was unlikely to increase to over £20,000 per QALY gained. The committee concluded that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained (see section 4.15 of the diagnostic guidance document). Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2017;21(29):1-236.
9	NHS Professional		The endorsement of routine use of ILR to detect asymptomatic paroxysmal AF, is premature because it assumes that there is clear evidence whether or not patients with 1-23 hour long episodes of device detected PAF which the patient is unaware of, should	Thank you for your comment which the committee considered. Recommendation 1.1 has been amended in the final guidance to clarify that Reveal LINQ is an option for use after cryptogenic stroke.

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			be anticoagulated. In fact since patients with device detected PAF have a different risk than patients who are aware of their PAF there are currently trials to try to establish who with device detected PAF should be anticoagulated. Perhaps ILRs should only be implanted in stroke patients who meet the criteria for the Artesia trial and whose doctors agree that if they detect episodes of <24 hrs, the patient should be counselled that we do not yet know whether they should be anticoagulated so it would be best if they joined the trial	The NICE clinical guidance on atrial fibrillation management recommends offering anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account. Clinical experts commented that because everyone who has had a cryptogenic stroke or TIA has a CHA_2DS_2-VASc score of at least 2, if an episode of atrial fibrillation of at least 30 seconds is seen these patients would routinely be offered anticoagulants. Ultimately it will be a clinician who decides if the episode of atrial fibrillation detected by the monitor is sufficient for anticoagulants to be offered, taking into account other clinical information. The committee noted the ongoing ARTESiA trial which has an estimated study completion date of December 2022 (NCT01938248). NICE reviews the evidence 3 years after publication of guidance to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

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10	Abbott Medical	1.1	There are data that show the benefit of implantable cardiac monitors for detecting atrial fibrillation, irrespective of brand. These data are: Merchant FM, Hoskins M, Musat D et al (2018). Atrial fibrillation hospitalizations are reduced after implantable cardiac monitor implant. Eur Heart J 39 (1): https://doi.org/10.1093/eurheartj/ehy566.P6592. Merchant FM, Passman R, Musat D et al (2018). Changes in stroke rates and oral anticoagulant prescription patterns after ICM implant. Heart Rhythm J 16 (5): https://doi.org/10.1016/j.hrthm.2019.04.017. Sakhi R, Theuns DAMJ, Szili-Torok T et al (2019). Insertable cardiac monitors: current indications and devices. Expert Rev Med Devices. 2019 Jan;16(1):45-55. doi: 10.1080/17434440.2018.1557046	Thank you for your comment which the committee considered. The EAG commented that it did not consider the papers highlighted by Abbott Medical to show equivalence between the different ICM devices for atrial fibrillation detection in cryptogenic stroke patients. The committee noted that the 2 Merchant et al. citations were for conference abstracts and that both assessed use of ICMs for atrial fibrillation management in people with known atrial fibrillation, rather than in a cryptogenic stroke population with suspected atrial fibrillation.

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			We would therefore suggest that the recommendation relate to ICMs and not be brand-specific.	

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THEME: Cryptogenic transient ischaemic attack

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11	British Association of Stroke Physicians		1) Evidence for cryptogenic TIA: the current wording treats TIA and IS in the same way. However it is worth pointing out that only selected TIAs were included in the Crystal AF trial – "Only TIAs with the following documented characteristics can be included: visible lesion on MRI or CT that fits the symptoms of the TIA and at least one of the following symptoms: speech problems, limb weakness or hemianopsia." (NEJM 2014; 370:2478-2486). Moreover, there are also recent data suggesting that AF detection in unselected TIA patients alone is lower than cohorts including both TIA and IS (In J Stroke 2017; 12: 33-45).	Thank you for your comment which the committee considered. Section 3.5 of the diagnostics guidance document has been updated to state the inclusion criteria for TIA for the CRYSTAL-AF trial as mentioned in the stakeholder's comment. The EAG explained that because of a lack of data split by TIA or stroke from CRYSTAL-AF, it was not possible to do an analysis for the yield of atrial fibrillation detected in these subgroups to inform the model. The committee considered it reasonable that the Reveal LINQ is an option for people with a cryptogenic TIA if non-invasive electrocardiogram (ECG) monitoring has been done, and a cardiac arrhythmic cause of stroke is still suspected. Recommendation 1.1 has been amended for the final guidance to specify that the Reveal LINQ is recommended as an

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				option to help to detect atrial fibrillation after cryptogenic stroke, including transient ischaemic attacks (TIA), only if non-invasive electrocardiogram (ECG) monitoring has been done, and a cardiac arrhythmic cause of stroke is still suspected.
12	British Association of Stroke Physicians		6) Evidence for cryptogenic TIA: the current wording treats TIA and IS in the same way. However it is worth pointing out that only selected TIAs were included in the Crystal AF trial – "Only TIAs with the following documented characteristics can be included: visible lesion on MRI or CT that fits the symptoms of the TIA and at least one of the following symptoms: speech problems, limb weakness or hemianopsia." (NEJM 2014; 370:2478-2486). Moreover, there are also recent data suggesting that AF detection in unselected TIA patients alone is lower than cohorts including both TIA and IS (In J Stroke 2017; 12: 33-45).	Thank you for your comment which the committee considered. Section 3.5 of the diagnostics guidance document has been updated to state the inclusion criteria for TIA for the CRYSTAL-AF trial as mentioned in the stakeholder's comment. The EAG explained that because of a lack of data split by TIA or stroke from CRYSTAL-AF, it was not possible to do an analysis for the yield of atrial fibrillation detected in these subgroups to inform the model. The committee considered it reasonable that the Reveal LINQ is an option for people with a

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Diagnostics Advisory Committee date: 27 February 2020

THEME: Cryptogenic transient ischaemic attack

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				cryptogenic TIA if non-invasive electrocardiogram (ECG) monitoring has been done, and a cardiac arrhythmic cause of stroke is still suspected. Recommendation 1.1 has been amended for the final guidance to specify that the Reveal LINQ is recommended as an option to help to detect atrial fibrillation after cryptogenic stroke, including transient ischaemic attacks (TIA), only if non-invasive electrocardiogram (ECG) monitoring has been done, and a cardiac arrhythmic cause of stroke is still suspected.
13	British Association of Stroke Physicians		11) P35 4.3: The population of TIAs in CRYSTAL AF is not broadly representative of the population of patients who would be referred for this test in the NHS. The population of TIA patients in the NHS – unless restricted to those with a definite ischaemic lesion of brain imaging – would be at lower risk of subsequent stroke. Similarly, it is not common practice (not is there evidence to support) transoesophageal echocardiography, screening for thrombophilia that were performed during the trial. In addition, patients with small strokes (<1cm, no otherwise defined) were excluded	Thank you for your comment which the committee considered. Recommendation 1.1 has been amended in the diagnostics guidance document to specify that Reveal LINQ is recommended as an option to help to detect atrial fibrillation after cryptogenic stroke, including transient ischaemic attacks (TIA), only if non-invasive electrocardiogram (ECG) monitoring has been done, and a

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				cardiac arrhythmic cause of stroke is still suspected.

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14	British Association of Stroke Physicians		4) What exactly does “non-invasive ECG” mean? There is currently lack of head-to-head randomised comparison between implantable cardiac monitoring vs. prolonged non-invasive cardiac monitoring. However, the EMBRACE AF trial showed clear superiority of a 30-day non-invasive approach vs. routine care. Also, in a previous systematic review of published cohorts, after initial screening, the yields of mobile cardia outpatient telemetry (15.3%) and external loop recording (16.2%) were comparable to that of the implantable loop recording (16.9%) at 6 months or 12 months (Lancet Neurol 2015; 14: 377-387). So at least the cost effectiveness between non-invasive vs. invasive cardiac monitoring is still unclear. 24h HOLTER does have low yield but that does not necessarily mean that there is convincing evidence that invasive monitoring should be recommended as “routine adoption” if routine ECG or 24 HOLTER does not show find any AF? A recent paper in Stroke (Stroke 2019; 50:2175-80) also showed the benefit of prolonged cardiac rhythm monitoring in secondary stroke prevention in patients with cryptogenic events.	Thank you for your comment which the committee considered. Non-invasive monitoring is any monitoring that can be used outside a hospital setting while a patient is going about their daily routines, but without an invasive procedure needed to implant a device. Clinical experts commented that the type and duration of non-invasive monitoring will vary by local availability across the NHS. Clinical experts emphasised that Reveal LINQ should only be used after all available non-invasive monitoring had been done, therefore these non-invasive monitors would not be replaced by implantable cardiac devices. However, longer duration non-invasive monitoring is likely to detect some cases of atrial fibrillation that shorter duration non-invasive monitoring would miss, and therefore if longer duration non-invasive monitoring were done there may be a lower yield of atrial fibrillation subsequently detected by implantable cardiac monitors. The EAG commented that, based on exploratory model analysis that assumed that anyone with atrial fibrillation in the first month of CRYSTAL-AF would not have had

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				an implantable cardiac monitor (that is, reducing the diagnostic yield for Reveal LINQ in the model), longer duration non-invasive monitoring of up to a month was unlikely to have a large impact on the cost effectiveness of Reveal LINQ (see section 4.17 of the diagnostics guidance document).
15	British Association of Stroke Physicians		9) What exactly does “non-invasive ECG” mean? There is currently lack of head-to-head randomised comparison between implantable cardiac monitoring vs. prolonged non-invasive cardiac monitoring. However, the EMBRACE AF trial showed clear superiority of a 30-day non-invasive approach vs. routine care. Also, in a previous systematic review of published cohorts, after initial screening, the yields of mobile cardia outpatient telemetry (15.3%) and external loop recording (16.2%) were comparable to that of the implantable loop recording (16.9%) at 6 months or 12 months (Lancet Neurol 2015; 14: 377-387). So at least the cost effectiveness between non-invasive vs. invasive cardiac monitoring is still unclear. 24h HOLTER does have low yield but that does not necessarily mean that there is convincing evidence	Thank you for your comment which the committee considered. Non-invasive monitoring is any monitoring that can be used outside a hospital setting while a patient is going about their daily routines, but without an invasive procedure needed to implant a device. Clinical experts commented that the type and duration of non-invasive monitoring will vary by local availability across the NHS. Clinical experts emphasised that Reveal LINQ should only be used after all available non-invasive monitoring had been done, therefore these non-invasive monitors would not be a replaced by implantable cardiac devices. However, longer duration non-invasive monitoring is likely to detect some cases of atrial fibrillation that

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			that invasive monitoring should be recommended as "routine adoption" if routine ECG or 24 HOLTER does not show find any AF? A recent paper in Stroke (Stroke 2019; 50:2175-80) also showed the benefit of prolonged cardiac rhythm monitoring in secondary stroke prevention in patients with cryptogenic events.	shorter duration non-invasive monitoring would miss, and therefore if longer duration non-invasive monitoring were done there may be a lower yield of atrial fibrillation subsequently detected by implantable cardiac monitors. The EAG commented that, based on exploratory model analysis that assumed that anyone with atrial fibrillation in the first month of CRYSTAL-AF would not have had an implantable cardiac monitor (that is, reducing the diagnostic yield for Reveal LINQ in the model), longer duration non-invasive monitoring of up to a month was unlikely to have a large impact on the cost effectiveness of Reveal LINQ (see section 4.17 of the diagnostics guidance document).
16	British Association of Stroke Physicians		The review of the evidence appears complete in relation to the specific devices included (BioMonitor 2-AF, Confirm Rx and Reveal LINQ). However, we consider this evidence to be insufficient by itself to justify the unqualified recommendation of the Reveal LINQ device for routine adoption into NHS practice, particularly since the study inclusion criteria were relaxed to include heterogeneous single-arm observational studies and the single randomised trial	Thank you for your comment which the committee considered. While single arm studies were included in the diagnostic assessment report, only data from the CRYSTAL-AF RCT were used in the economic model to assess the cost effectiveness of the devices. Section 3.8 of the diagnostics guidance document notes that the committee were aware that this trial was sponsored by

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			in a cryptogenic stroke population was sponsored by the manufacturer and the authors reported income from this company. There are numerous other devices and technologies for detecting AF following cryptogenic stroke over varying durations, and these warrant consideration in the comparator. The comparator is "No further testing after outpatient ambulatory ECG monitoring"; the diagnostic yield of outpatient ambulatory ECG monitoring is not adequately covered within the evidence presented. For example, the EMBRACE study (Gladstone et al, NEJM 2014; 370: 2467-2477) reports a substantial incremental AF detection rate for ambulatory cardiac monitoring using a 30-day event recorder compared with a 24-hour Holter monitor after at least one 24 hour period of Holter monitoring before randomisation. One of the ongoing studies mentioned in the consultation document (PERDIEM, NCT02428140) is particularly relevant to this question, as this study is	Medtronic, and that the authors of publications for this study reported employment, grants and personal fees from this company. The comparator for this assessment, as set out in the published scope, is no further monitoring for atrial fibrillation (after at least 24 hours of outpatient external ambulatory ECG monitoring that has not detected atrial fibrillation) [underlining added]. Because CRYSTAL-AF was the source of data used for economic modelling, the extent of previous non-invasive monitoring for atrial fibrillation done reflected what was done in this study (up to 24 hours). Clinical experts emphasised that Reveal LINQ would only be used after all available non-invasive monitoring had been done, therefore these non-invasive monitors would not be replaced by implantable cardiac devices. However, longer duration non-invasive monitoring is likely to detect some cases of atrial fibrillation that shorter duration non-invasive monitoring would miss, and therefore if longer duration non-invasive monitoring were done there may be a lower yield of atrial fibrillation

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			comparing the Reveal LINQ device with a 30-day external event-triggered loop recorded and has completed enrolment, with a primary outcome of cost-effectiveness at 12 months. This is particularly relevant since there are assumptions within the cost effectiveness model that may not hold (see question 2 below).	subsequently detected by implantable cardiac monitors. The EAG commented that, based on exploratory model analysis that assumed that anyone with atrial fibrillation in the first month of CRYSTAL-AF would not have had an implantable cardiac monitor (that is, reducing the diagnostic yield for Reveal LINQ in the model), longer duration non-invasive monitoring of up to a month was unlikely to have a large impact on the cost effectiveness of Reveal LINQ (see section 4.17 of the diagnostics guidance document).
17	British Association of Stroke Physicians		The summaries do seem largely reasonable but there is considerable uncertainty about the numbers used to populate the model, for example: - The rate of AF detection was low in the control arm of CRYSTAL-AF (only 1.4% after 6 months). If this were higher where improved non-invasive methods of AF detection are used, this would likely affect estimates of clinical and cost-effectiveness. While variations of the economic model are described, none seem to include its robustness to differences in AF	Thank you for your comment which the committee considered. The committee noted that longer duration non-invasive monitoring is likely to detect some cases of atrial fibrillation that shorter duration non-invasive monitoring would miss, and therefore if longer duration non-invasive monitoring were done there may be a lower yield of atrial fibrillation subsequently detected by implantable cardiac monitors. The EAG commented that, based on exploratory model analysis that assumed

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			detection in conventional follow-up. It would be helpful to see results of such an analysis, informed by other studies of cryptogenic stroke	that anyone with atrial fibrillation in the first month of CRYSTAL-AF would not have had an implantable cardiac monitor (that is, reducing the diagnostic yield for Reveal LINQ in the model), longer duration non-invasive monitoring of up to a month was unlikely to have a large impact on the cost effectiveness of Reveal LINQ (see section 4.17 of the diagnostics guidance document).
18	British Cardiovascular Society		It would also be helpful if the recommendation could clarify “non-invasive ECG monitoring". The guidance does not clarify what constitutes an appropriate length of time that this should be done for, and what would constitute a significant episode of atrial fibrillation detected with this technique.	Thank you for your comment which the committee considered. Clinical experts highlighted that it is important that all available non-invasive ECG monitoring is done first before Reveal LINQ is considered, and that the type and duration of non-invasive monitoring will vary by local availability across the NHS. In terms of what would constitute a significant episode of atrial fibrillation, this would be a clinical decision made by NHS clinicians in terms of whether they

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				thought an episode of atrial fibrillation was significant enough to offer anticoagulants.

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19	BIOTRONIK SE & Co KG	General	BIOTRONIK would like to thank NICE for the opportunity to comment on the Diagnostics consultation document. BIOTRONIK's main concern refers to how NICE have considered fundamental physiological knowledge when assessing the submitted clinical evidence. Other comments refer to the misinterpretation of data and of technical capabilities of one of the ICMs under assessment.	Thank you for your comment which the committee considered.
20	BIOTRONIK SE & Co KG	3.21	In commenting on the ECG information used as feed in the validation study comparing Reveal LINQ and of BioMonitor devices this section states: "Of the participants, 70% had a history of paroxysmal atrial fibrillation. The rest had a history of persistent atrial fibrillation." The wording gives the impression that (a) persistent AF information was used in the validation study and (b) that this would be relevant for the results.	Thank you for your comment which the committee considered. The EAG commented that the population in the validation study was described as having "a history of paroxysmal AF in 70% of the enrolled cohort and the rest of the cohort presented with a history of persistent AF". It also acknowledged that the report states, "Those presenting with long-standing persistent or permanent AF were excluded." The EAG therefore considered that the information in the publication was contradictory and is unclear as to the population in the validation study.

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			Re (a): This is a misinterpretation of the data submitted by BIOTRONIK. All ECG data fed into the devices as part of the technical validation study had a duration less than 48h (median 27.5h) (see section 3.4 in the study report by Micro Systems Engineering, 2019). Thus, the ECG data represent paroxysmal AF episodes only, as defined in the 2016 ESC guidelines (Kirchhof et al (2016) ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 37(38): 2893 – 2962). Information on persistent AF episodes was not used in the validation study. Re (b): The terms 'paroxysmal' and 'persistent' refer to whether AF episodes terminate spontaneously or not. They define the patient's status, and are not characteristics of the episodes themselves. See the 2016 ESC guidelines as follows: *[Figure removed]* (Reproduced from (Kirchhof et al (2016) ESC Guidelines for the management of atrial fibrillation developed in	Further text has been added to section 3.21 of the diagnostics guidance document to include the stakeholder's explanation of the population included in the report, and the EAG's comment on this.

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			collaboration with EACTS. Eur Heart J 37(38): 2893 – 2962.)) **Therefore, our request is for an addition to the text clarifying that all information used in the technical validation study and the study findings represent paroxysmal AF episodes, and for not rejecting the submitted evidence based on such grounds.**	
21	BIOTRONIK SE & Co KG	3.41	"The EAG highlighted that the performance of the devices depends on the patient population, …. Therefore, the results from these studies do not necessarily represent the devices' performance in people with cryptogenic stroke." This statement refers to evidence generated in non-cryptogenic stroke populations, rejecting all such submitted data. Diagnostic yield is the product of two components, prevalence or incidence (here: of AF in the population) and device sensitivity (as proportion of true AF episodes that are detected). The CRYSTAL-AF study has shown a	Thank you for your comment which the committee considered. The committee considered the technical report submitted by Biotronik at the last consultation at the previous committee meeting on 27 November 2019. This was recorded in section 4.6 of the updated diagnostic consultation document (and remains in the same section in the diagnostics guidance document). Studies submitted by Biotronik reporting the diagnostic accuracy of the BioMonitor device were also included in the EAG's original report (see section 3.4.2 of the diagnostic assessment report). This was considered by the committee (see section 3.45, 3.46 and 3.27 of

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			meaningful diagnostic yield but its two components remain unknown because only their product has been measured. Therefore, CRYSTAL AF has not shown device performance. Device performance can only be measured in a population with sufficient AF burden and with a reference in place, e.g. 24 h surface ECG, in a sufficient proportion of included subjects. Therefore, the sensitivity of ICMs for AF (including the device used in CRYSTAL AF) had to be tested in patients with paroxysmal or persistent AF. The sensitivity observed in these studies can be used to inform on the sensitivity in stroke patients because the heart rhythm is autonomous, and the ECG is not modified by dysfunctions in the brain such as the local damage caused by a stroke. **There is no physiologically plausible reason why an ICM that can detect AF in patients without stroke would not do so in a patient with a history of stroke.** Further, ICMs have software algorithms that react to electrophysiological signals from the heart. These	the diagnostics guidance document); however, because the diagnostic accuracy data were unpublished and were provided as academic or commercial in confidence these details could not be reported in this guidance. The EAG commented that no new data were presented for the committee meeting on 27 February 2020 and therefore as stated in the EAG's original report, the EAG still considered there to be insufficient clinical evidence to conclude that all ICMs would be equally effective at detecting atrial fibrillation in people with cryptogenic stroke. As noted in the stakeholder's comment, diagnostic yield includes the sensitivity of the device to detect atrial fibrillation. Therefore, if the sensitivity of implantable cardiac monitors differs, then so could their diagnostic yield. The committee did not consider that the technical report provided by Biotronik showed that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population. Clinical experts

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			algorithms behave in the same way in whatever person presents such signal. Thus, the population in which device accuracy of ICMs is measured is largely irrelevant (apart from observing sufficient AF burden and have a reference in place, as discussed above). The population matters when assessing the need for ICMs in general but device accuracy can be compared using other study samples and study techniques. Lastly, AF is a common endpoint of cardiac disease. All initial treatments for rhythm disorders including AF target the heart and not any other organ system. This supports the notion that AF is of cardiac origin, and its occurrence is independent of an existing stroke. **For the reasons above, our request is for NICE to consider submitted evidence on device performance (sensitivity) generated using ECG information from other patient groups than the one covered in the assessment, namely the validation study submitted by BIOTRONIK which established equal performance of BioMonitor 2 and Reveal LINQ (AF episode**	commented that it is uncertain that the ability of implantable cardiac monitors to detect atrial fibrillation in non-cryptogenic stroke is generalisable to a cryptogenic stroke population, noting that atrial fibrillation that is undetected after cryptogenic stroke is asymptomatic and, based on CRYSTAL-AF data, is likely to be short in duration. While it was likely that BioMonitor 2-AF and Confirm Rx would detect atrial fibrillation in a cryptogenic stroke population, in the absence of data on performance in this population it is uncertain that they would be as effective as the Reveal devices. The committee decided not to change its previous conclusion that there is too much uncertainty over whether data generated using a Reveal device in a cryptogenic stroke population can be used to show the performance of the BioMonitor 2 AF or Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke. Therefore, the committee concluded that evidence from the CRYSTAL AF study

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			sensitivity of 78% and 79% for BioMonitor2-AF versus Reveal LINQ, respectively, and patient averaged PPV of 98.7% and 99.7%, respectively). **Our request is also for NICE to correct its implication that pre-existing or concomitant non-cardiac conditions are relevant for assessing ICM device performance (specificity). This applies to the entire document, not just to section 3.41.**	could not be applied to these devices (see section 4.6 of the diagnostics guidance document).
22	BIOTRONIK SE & Co KG	4.6	"The study also used a longer threshold for AF than CRYSTAL-AF …" This comment refers to the ECG data used in the technical comparison of BioMonitor2-AF and Reveal LINQ (Micro Systems Engineering, 2019, submitted by BIOTRONIK). The conclusion that Reveal XT is capable of detecting AF episodes as short as 30 seconds is likely to be a misinterpretation of the CRYSTAL-AF publication. The study defined AF episodes as an "episode of irregular	Thank you for your comment which the committee considered. The EAG noted that in CRYSTAL-AF, episodes of AF were required to be a minimum of 30 seconds whereas in the technical comparison study of BioMonitor2-AF and Reveal LINQ a two-minute threshold was used. The EAG considers that there is some uncertainty about the exact device capabilities in this regard.

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			heart rhythm, without detectable P waves, lasting more than 30 seconds". While this definition has been used as a threshold within the study, it is no clear indication of the technical capability of Reveal XT to detect AF episodes as short as 30 seconds. The study itself reports mean and maximum AF duration as categorized data, aggregating episodes of 0-2 minutes duration without further detailing durations below 2 minutes. (Sanna et al (2014) Cryptogenic Stroke and Underlying Atrial Fibrillation, NEJM 370 (26) 2478 – 2486) Also the relevant Reveal XT technical manuals do not confirm the ability to detect AF episodes as short as 30 seconds. Instead, they state that (a) the Marker Channel annotations used in the Reveal XT software can only describe the end of AT and AF detections of 'at least 2 min of atrial arrhythmia' (Medtronic Inc, Reveal XT 9529 Clinician Manual, M943798A001 REV. C, 2014, pg 29), (b) for AT/AF detection sensing and performance tests only 'AT/AF episodes >2 min in duration were considered from standard, published databases' and that the 'device	Given this uncertainty, reference to the length of threshold for atrial fibrillation used in the technical validation study has been removed from section 4.6 of the diagnostics guidance document.

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			was optimized to detect episodes longer than 2 min.' (Medtronic Inc, Reveal XT 9529 Clinician Manual, M942691A001 REV. D, 2013, pg 81), and (c) 'AT/AF episodes are detected using an automatic algorithm based on the pattern of R-wave interval variability within 2-minute periods' (Medtronic Inc, Reveal XT 9529 Clinician Manual, M943798A001 REV. C, 2014, pg 47). Therefore, NICE' request for evidence from studies using a definition of AF of longer or equal to 30 seconds only seems to be unwarranted. There is no indication whatsoever available from literature or device manuals that the Reveal XT could technically detect episodes as short as 30 seconds. The only clear indication, based on the CRYSTAL-AF study and the device manual, is for a capability for detecting AF episodes as short as two minutes. This technical capability is met by BIOMONITOR III, which offers an AF detection confirmation time of one minute.	

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			Our request is for the duration of AF episodes not being considered in NICE' decision making and for the evidence submitted by BIOTRONIK not to be rejected based on such grounds.	
23	BIOTRONIK SE & Co KG	4.6	"The study also used a longer threshold for AF than CRYSTAL-AF …" In addition to the technical aspects discussed before, a recent systematic evidence review and meta-analysis of 28 ICM studies found no positive association between cumulative AF detection and the time threshold programmed for AF definition (30 secs, 2 mins, 6 mins) (Tsivgoulis et al (2019) Duration of Implantable Cardiac Monitoring and Detection of Atrial Fibrillation in Ischemic Stroke Patients: A Systematic Review and Meta-Analysis, J Stroke 21(3):302-311). The authors state 'the results of subgroup analysis, regarding the time threshold used for AF definition, do not confirm the association of improved ICM performance with increased duration of AF episodes' (pg 307, see also Supplementary Figure 13, reproduced in the following).	Thank you for your comment which the committee considered. The EAG reviewed the paper cited and did not consider it suitable for drawing conclusions regarding the impact of atrial fibrillation threshold on atrial fibrillation detection rates as there were high levels of statistical and clinical heterogeneity in the included studies; the I^2 in the subgroup analyses for the >30 second and >2 minute AF threshold subgroups were 89% and 97%, respectively. As noted in the response to the above comment, reference to the length of threshold for atrial fibrillation used in the technical validation study has been removed from section 4.6 of the diagnostics guidance document.

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			[Figure removed] In conclusion, based on current scientific evidence, there is no association of ICM performance and duration of AF episodes, and thus, no attention needs to be given to the definition of threshold for AF in the different studies and no rejection of evidence on such grounds is warranted. **Our request is for the duration of AF episodes not being considered in NICE' decision making and for the evidence submitted by BIOTRONIK not to be rejected based on such grounds.**	
24	BIOTRONIK SE & Co KG	4.6	"The study …. was not done in a cryptogenic stroke population, … " See comments to section 3.41 before. **Our request is for the evidence submitted by BIOTRONIK not to be rejected based on such grounds.**	Thank you for your comment which the committee considered.

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25	Abbott Medical	1.1	The transferability of CRYSTAL-AF data from REVEAL XT (used in the trial) to REVEAL LINQ is an assumption upon which the whole assessment rests and is critical to recommendation 1.1. There is no certainty that REVEAL XT data can be assumed to transfer to REVEAL LINQ and it stated in section 3.48 of the draft guidance that a modified algorithm has now been incorporated into REVEAL LINQ. If transfer of data is acceptable between REVEAL XT and REVEAL LINQ, it should also be acceptable between REVEAL XT and other devices, like Confirm RX. In the DETECT AF study, Confirm (predicate of Confirm Rx) demonstrated that sensitivity was 100%, PPV was 64.0%, SP was 85.7%, and NPV was 100% for detecting AF in per patient analysis. When using a per episode analysis, sensitivity was 94.0% and PPV was 64.0%. With an AF duration analysis, the SE was 83.9%, PPV was 97.3%, SP was 99.4% with an NPV of 98.5%.	Thank you for your comment which the committee considered. The DETECT AF study mentioned in the stakeholder's comment was discussed in the EAG's original report (see section 3.4.1 of the diagnostics assessment report) and in the diagnostics guidance document (see sections 3.43 and 3.44). The study did not report results for a cryptogenic stroke population. The committee did not change its conclusion that while it is feasible that data from Reveal XT is likely to apply to the updated version from the same manufacturer, Reveal LINQ, there is too much uncertainty over whether the data can be used to show the performance of the BioMonitor 2 AF or Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke (further description of the rationale for this can be found in section 4.16 of the diagnostics guidance document). Therefore, the recommendations have not been changed.

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			Similar transferability of DETECT AF data from Confirm to Confirm Rx should be applicable. Nölker G, Mayer J, Boldt LH et al (2016). Performance of an Implantable Cardiac Monitor to Detect Atrial Fibrillation: Results of the DETECT AF Study. J Cardiovasc Electrophysiol. 2016 Dec;27(12):1403-1410. doi: 10.1111/jce.13089 We would therefore recommend that Section 1.1 read "implantable cardiac monitors are recommended for routine adoption to help to detect atrial fibrillation after cryptogenic stroke…" given the issue with the transferability of the data from device to device. We note that the DCD carries a title of "Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke", which is not brand-specific.	
26	Abbott Medical	1.1	There is recent evidence that Confirm Rx is effective in detecting atrial fibrillation in cryptogenic stroke patients. A prospective multicentre randomised study enrolled patients with cryptogenic stroke (65% of the enrolled patients) and compared the ability of Reveal LINQ vs.	Thank you for your comment which the committee considered. The committee considered the Yokokawa et al. (2019) citation. It noted that this is a conference abstract with very limited methodological detail on the study

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			Confirm Rx to detect atrial fibrillation and the time between event detection and data availability for clinician review. The study demonstrated that time to data transmission and availability for clinician review was significantly faster with Confirm Rx compared to Reveal LINQ, while AF detection accuracy was equivalent between the two devices. (Yokokawa M, Jaffe B, Ip R et. al. Efficiency and accuracy of arrhythmia detection using implantable cardiac monitor: A prospective multicenter randomized clinical trial comparing Reveal LINQ and Confirm Rx. Euro Heart J, 40 (S1). https://academic.oup.com/eurheartj/article-abstract/40/Supplement_1/ehz746.0591/5597824. Accessed 17 January 2019). Recent publications show that the latest algorithm updates to Confirm Rx devices further improve the AF detection accuracy. (Quartieri F, Cauti FM, Calo L, et al. Retrospective analysis of Confirm Rx SharpSense technology using real-world data from the SMART registry. Journal of Arrhythmia. 2019; 35(Suppl. 1): 4-75. DOI: 10.1002/joa3.12266).	provided. Text has been added to section 3.51 of the diagnostics guidance document to describe this additional study. The EAG commented that the device accuracy in terms of atrial fibrillation detection is lower than that of the Reveal LINQ (Confirm RX 44% versus Reveal LINQ 55%). Because of a lack of detail in the conference abstract it was not clear why the number of events detected in the Reveal LINQ and Confirm Rx arms were so different. The manufacturer of the Confirm Rx stated that this was an investigator-initiated study without company involvement, so they were unable to provide clarification on study methodology. The committee considered that there was insufficient information available about this study to use it to assess whether Reveal LINQ and Confirm Rx had similar effectiveness to detect atrial fibrillation in a cryptogenic stroke population (see section 4.19 of the diagnostics guidance document). The EAG commented that the Quartieri et al. work cited was also a conference abstract. It acknowledged that

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				the publication suggests improvements to the accuracy of the Confirm RX in atrial fibrillation detection, although there are no specific cryptogenic stroke subgroup data presented.
27	Abbott Medical	3.14	The comment "Reveal XT increased atrial fibrillation detection across all pre-specified subgroups" relates to REVEAL XT and may not be accurate for REVEAL LINQ. If transfer of data is acceptable between REVEAL XT and REVEAL LINQ, it should also be acceptable between REVEAL XT and other devices like Confirm Rx. (See comment 1) It is stated in the DCD that Medtronic had said that the number of false positive alerts varies depending on the device model used, and the configuration for detection (including episode duration) that is programmed by the operator.	Thank you for your comment which the committee considered.
28	Abbott Medical	3.15	It is noted that "around 70% to 80% (of the total number of people with atrial fibrillation detected in a study) are diagnosed by 6 months, and a small number after a year of monitoring". Why then does battery life beyond two years feature in a cost effectiveness analysis (if only a	Thank you for your comment which the committee considered. The quoted text is in reference to the single-arm observational studies reported in the diagnostics

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			small number of primary AF events were detected after year 1). It is important to note that of the 221 enrolled patients, only 4 were detected after the 24 month time frame.	assessment report, rather than the CRYSTAL-AF RCT that was used in the economic model. As noted in the stakeholder's comment, additional cases of atrial fibrillation were detected in CRYSTAL-AF after 2 years. The EAG commented that battery life is considered in the analysis because CRYSTAL-AF provided data for 3 years' worth of monitoring. Confirm RX's battery life is two years and thus would not pick up any of the events recorded in year three of CRYSTAL-AF.
29	Abbott Medical	3.20	It is noted that "Medtronic had said that the number of false positive alerts varies depending on the device model used, and the configuration for detection (including episode duration) that is programmed by the operator". This is an acknowledgement that REVEAL LINQ gives an unpredictable number of false positive alerts, which also indicates that it performs differently from REVEAL XT in the detection of AF in cryptogenic stroke. If transfer of data is acceptable between REVEAL XT and REVEAL LINQ, it should also be acceptable	Thank you for your comment which the committee considered. The committee did not change its conclusion that while it is feasible that data from Reveal XT is likely to apply to the updated version from the same manufacturer, Reveal LINQ, there is too much uncertainty over whether the data can be used to show the performance of the BioMonitor 2 AF or Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke.

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			between REVEAL XT and other devices like Confirm Rx. (See comment 1)	
30	Abbott Medical	4.6	The DCD states that "The CRYSTAL-AF study used Reveal XT, a predecessor model of Reveal LINQ. Changes have been made to the atrial fibrillation detection algorithm that is now used in Reveal LINQ". This is a clear statement that the AF detection algorithm used in Reveal LINQ is different to that in REVEAL XT. This supports our view expressed in comment 1 that if transfer of data is acceptable between REVEAL XT and REVEAL LINQ, it should also be acceptable between REVEAL XT and other devices like Confirm Rx.	Thank you for your comment which the committee considered. The committee did not change its conclusion that while it is feasible that data from Reveal XT is likely to apply to an updated version from the same manufacturer, Reveal LINQ, there is too much uncertainty over whether the data can be used to show the performance of the BioMonitor 2 AF or Confirm Rx, which use different algorithms, to detect atrial fibrillation in people who have had a cryptogenic stroke. Clinical experts said that the atrial fibrillation detection algorithms in other manufacturers' devices may use the same features of an ECG to detect potential atrial fibrillation. But how these features are used to determine if atrial fibrillation is likely to be present, or to classify an arrythmia as atrial fibrillation or another type of arrythmia, is likely to differ between devices (see section 4.6 of the guidance document).

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Comment number	Name and organisation	Section number	Comment	NICE response
31	Abbott Medical	4.6	The DCD notes that it is considered that "….there is too much uncertainty over whether the data can be used to show the performance of the BioMonitor 2-AF or Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke. Therefore, the committee did not accept that evidence from the CRYSTAL-AF study could be applied to these devices." The algorithm of ICM is conceived in order to capture atrial fibrillation. AF after cryptogenic stroke is part of the AF detection algorithm, which was shown in a recent RCT to be equivalent between Reveal LINQ and Confirm Rx (Yokokawa M, Jaffe B, Ip R et al (2019). Efficiency and accuracy of arrhythmia detection using implantable cardiac monitor: A prospective multicenter randomized clinical trial comparing Reveal LINQ and Confirm Rx. Euro Heart J, 40(S1). https://academic.oup.com/eurheartj/article-abstract/40/Supplement_1/ehz746.0591/5597824. Accessed 17 January 2019).	Thank you for your comment which the committee considered. The committee noted that Yokokawa et al. (2019) was only available as a conference abstract with limited detail on methodology, and it was not clear why the number of events detected in the Reveal LINQ and Confirm Rx arms were so different. The manufacturer of the Confirm Rx stated that this was an investigator-initiated study without company involvement, so they were unable to provide clarification on study methodology. The committee considered that there was insufficient information available about this study to use it to assess whether Reveal LINQ and Confirm Rx had similar effectiveness to detect atrial fibrillation in a cryptogenic stroke population. The EAG commented that the device accuracy in terms of atrial fibrillation detection is lower than that of the

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Comment number	Name and organisation	Section number	Comment	NICE response
			It is therefore unreasonable to conclude that there is too much uncertainty over whether the data can be used to show the performance of Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke. If transfer of data is acceptable between REVEAL XT and REVEAL LINQ, it should also be acceptable between REVEAL XT and other devices like Confirm Rx. (See comment 1)	Reveal LINQ (Confirm RX 44% versus Reveal LINQ 55%). The committee did not change its conclusion that while it is feasible that data from Reveal XT is likely to apply to the updated version from the same manufacturer, Reveal LINQ, there is too much uncertainty over whether the data can be used to show the performance of the BioMonitor 2 AF or Confirm Rx to detect atrial fibrillation in people who have had a cryptogenic stroke.

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32	BIOTRONIK SE & Co KG	1.3 and 5.1	"Further research is recommended to assess diagnostic yield (a measure of how many people with atrial fibrillation are diagnosed) of these devices for atrial fibrillation when used in people who have had a cryptogenic stroke (see section 5.1)." "Further research is recommended to assess the diagnostic yield of the BioMonitor 2-AF and Confirm Rx (or later devices) for atrial fibrillation when used in people who have had a cryptogenic stroke…" Essentially, NICE seem to expect current and future manufacturers of ICM devices to repeat the CRYSTAL-AF study to prove that their devices perform equal to each other (or Reveal LINQ). The CRYSTAL-AF study has furthered clinical knowledge about the true incidence of atrial fibrillation (AF) in patients with prior cryptogenic stroke, one element of 'diagnostic yield'. It has not contributed any data on the diagnostic accuracy (the other element of 'diagnostic yield') for the Reveal XT, the predecessor	Thank you for your comment which the committee considered. The committee concluded that there was a lack of acceptable evidence showing that BioMonitor 2-AF or Confirm Rx (or predecessor versions) had comparable effectiveness to Reveal devices for the detection of atrial fibrillation in people with cryptogenic stroke. It recalled that diagnostic yield data produced by using a Reveal device had been used for cost effectiveness modelling for this assessment. The committee noted the difficulties in providing adequate comparative data on the performance of the different implantable monitors to detect atrial fibrillation in a person with cryptogenic stroke; that is, to show similar performance to Reveal devices for detecting atrial fibrillation in this population. It further noted that a randomised controlled trial that compared Reveal LINQ and Confirm Rx in a population that was mostly people with cryptogenic stroke had been highlighted at consultation on the draft guidance (Yokokawa et al. 2019; see section 3.51 of the diagnostics guidance document). The committee

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			model of Reveal LINQ used in the study. In fact, during the evaluation by NICE, device accuracy (as sensitivity) had to be established using various other data sets. We believe that repeating the CRYSTAL-AF study is redundant as it would not contribute any new knowledge on AF prevalence or on the performance of individual ICM models. Therefore, the request as currently worded in the draft document is not warranted. **The request should be modified and ask for device performance data only, not for repeating a collection of epidemiological data on asymptomatic paroxysmal AF, which essentially is the contribution of CRYSTAL-AF.** See also our comments to section 3.41, please.	concluded that this work did show the feasibility of doing trials to compare the effectiveness of different implantable cardiac monitors to detect atrial fibrillation in a cryptogenic stroke population (see section 4.19 of the diagnostics guidance document).
33	Arrhythmia Alliance	General	This recommendation is welcomed however our concern is that is recommends one specific manufacturer. Is there a reason why it does not just refer to ICM's or mention other manufacturers. Our concern is that some clinician's and CCG's may	Thank you for your comment which the committee considered. Only Reveal LINQ is recommended in the diagnostics guidance (see recommendation 1.1). The committee

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			interpret that this is the only ICM recommended by NICE and therefore patients could be disadvantaged if they can no longer access this diagnostic therapy in their hospital if the hospital does not use Medtronic.	concluded that there is not enough evidence to recommend the routine adoption of BioMonitor 2 AF (or its successor device BIOMONITOR III) or Confirm Rx to help to detect atrial fibrillation after cryptogenic stroke. Further research is recommended to assess the diagnostic yield (a measure of how many people with atrial fibrillation are diagnosed) of these devices for atrial fibrillation when used in people who have had a cryptogenic stroke (see section 1.3 of the diagnostics guidance document). Clinical experts commented that there would be relatively few barriers to hospitals that do not currently use Medtronic systems to start using these systems for this indication.
34	NHS Professional		It is unfair for NICE to promote one company's product only, particularly when other companies have equally good, if not better, products which have been available for many years.	Thank you for your comment which the committee considered. The committee concluded that there is not enough evidence to recommend the routine adoption of BioMonitor 2 AF (or its successor device BIOMONITOR III) or Confirm Rx to help to detect atrial fibrillation after

Comment number	Name and organisation	Section number	Comment	NICE response
			Furthermore, for NICE to propose such a monopoly is not in the interest of the patient or the medical community.	cryptogenic stroke. This was because the only study that compared use of an implantable cardiac monitor to no use of such devices used a Reveal device (a predecessor of the current Reveal LINQ): the CRYSTAL-AF study. The committee concluded that CRYSTAL-AF data can be used to assess how well Reveal LINQ detects atrial fibrillation in people who have had a cryptogenic stroke, but not BioMonitor 2 AF or Confirm Rx (see section 4.6 of the diagnostics guidance document for further details and rationale). Therefore, no data on the performance of the BioMonitor or Confirm Rx were available to assess their cost effectiveness. Further research was recommended to assess the diagnostic yield (a measure of how many people with atrial fibrillation are diagnosed) of these devices for atrial fibrillation when used in people who have had a cryptogenic stroke (see section 1.3 of the diagnostics guidance document). NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified.

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				However, NICE may review and update the guidance at any time if significant new evidence becomes available. If further data on the devices become available, the guidance may be reviewed.
35	British Association of Stroke Physicians		2) Evidence at younger ages: Crystal AF only included patients aged 40 years or above, whereas the current wording seems to indicate that the evidence is there for everyone.	Thank you for your comment which the committee considered. The committee considered the population enrolled in the CRYSTAL-AF study and concluded that it broadly represents people with cryptogenic stroke in the NHS, although there may be some people younger than 40 who are seen in practice. It did not consider that it was appropriate to limit the use of the Reveal LINQ to people over a certain age. Therefore, no age restrictions have been included in the recommendation for the Reveal LINQ.
36	British Association of Stroke Physicians		3) Current evidence is mainly for patients with cryptogenic stroke who are thought to be at increased risk of AF.	Thank you for your comment which the committee considered.

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				The recommended use of the Reveal LINQ is limited to people who have cryptogenic stroke.
37	British Association of Stroke Physicians		7) Evidence at younger ages: Crystal AF only included patients aged 40 years or above, whereas the current wording seems to indicate that the evidence is there for everyone.	Thank you for your comment which the committee considered. The committee considered the population enrolled in the CRYSTAL-AF study and concluded that it broadly represents people with cryptogenic stroke in the NHS, although there may be some people younger than 40 who are seen in practice. It did not consider that it was appropriate to limit the use of the Reveal LINQ to people over a certain age. Therefore, no age restrictions have been included in the recommendation for the Reveal LINQ.
38	British Association of Stroke Physicians		8) Current evidence is mainly for patients with cryptogenic stroke who are thought to be at increased risk of AF.	Thank you for your comment which the committee considered. The recommended use of the Reveal LINQ is limited to people who have cryptogenic stroke.

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39	British Cardiovascular Society		The BCS and BHRS are very supportive of any evidenced based intervention to reduce the burden of cardiovascular disease. We also commend NICE for wanting to accelerate interventions to help improve patient outcomes after stroke. We recognise the huge impact of strokes on patients, their families and the resulting financial implications both on health systems, patients and the wider community. However, on balance we feel that this subject should ideally be explored with further research or as a compromise, all patients being recruited into a formal	Thank you for your comment which the committee considered.

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			registry. We feel that this is an area well suited for a NICE research recommendation . In response to the specific question asked by the consultation: • Has all of the relevant evidence been taken into account? YES • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Probably not (NO) • Are the recommendations sound, and a suitable basis for guidance to the NHS? probably not (NO)	
40	NHS Professional		· Are the recommendations sound, and a suitable basis for guidance to the NHS? We would contend that the recommendations should be much more qualified, specifically in relation to the type and duration of ambulatory ECG monitoring required before a Reveal LINQ device is used.	Thank you for your comment which the committee considered. Clinical experts emphasised that Reveal LINQ would only be used after all available non-invasive monitoring had been done, therefore these non-invasive monitors would not be replaced by implantable cardiac devices. However, longer duration non-invasive monitoring is likely to detect some cases of atrial fibrillation that

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			It would be preferable to include a comparison between ICRs and more prolonged non-invasive ambulatory monitoring if possible. If on further review of the evidence a meaningful comparison is not possible, we would suggest that this recommendation should be accompanied by a statement that both ICRs and prolonged non-invasive monitoring devices have been shown to be superior to brief (24 hour) Holter monitoring in terms of AF detection after cryptogenic stroke, but that direct comparisons are not possible on the basis of current data. Research Recommendations should include the need for further evidence comparing the effectiveness of ICRs with non-invasive devices (a question that is the subject of ongoing studies	shorter duration non-invasive monitoring would miss, and therefore if longer duration non-invasive monitoring were done there may be a lower yield atrial fibrillation subsequently detected by implantable cardiac monitors. The EAG commented that, based on exploratory model analysis that assumed that anyone with atrial fibrillation in the first month of CRYSTAL-AF would not have had an implantable cardiac monitor (that is, reducing the diagnostic yield for Reveal LINQ in the model), longer duration non-invasive monitoring of up to a month was unlikely to have a large impact on the cost effectiveness of Reveal LINQ (see section 4.17 of the diagnostics guidance document). Clinical experts highlighted that it is important that all available non-invasive ECG monitoring is done first before Reveal LINQ is considered, and that the type and duration of non-invasive monitoring will vary by local availability across the NHS.
41	NHS Professional		1) Are the trials clearly generalisable to NHS practice? (probably not)	Thank you for your comment which the committee considered.

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			2) Is there the potential for 'mission creep' from the draft guidance (Yes) 3) Is there the currently the opportunity to require better real world evidence of cost effectiveness before issuing recommendations that in practice will allow widespread use (Yes). 4) Is there an opportunity cost in the increased rates of ILR implantation and follow up that will follow? (Yes) Might this actually compromise other cardiac services particularly given limited resources of physiologists? (Yes) 5) Is this recommendation likely to increase difficulties funding cardiology services and reduce sustainability? (yes)	

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42	British Cardiovascular Society		There are also significant upfront costs from this strategy. These include the initial cost of the device but also implications in delivering an implant service and running the follow up of these patients.	Thank you for your comment which the committee considered. The EAG explained that costs related to purchasing the implantable cardiac monitors, implanting and removing the devices and the cost of follow-up appointments have been included in the economic model. Full detail on the costs included in the model can be found in the diagnostics assessment report starting on page 92.
43	NHS Professional		On a minor note, the implant cost of £24.17 is an underestimate even if the operator time is only 10 minutes and ignores any administrative and other costs. (It also ignores costs to patient eg transport/parking)	Thank you for your comment which the committee considered. The EAG explained that they investigated the effect of increasing the cost of implanting the devices in a sensitivity analysis. Using a higher cost of implantation (£34) had only a small effect on cost effectiveness estimates (see page 107 in the diagnostics assessment report). The EAG therefore concluded that even if this

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				cost has been underestimated, this is very unlikely to have a significant impact on cost effectiveness estimates. The perspective adopted on costs in NICE diagnostics guidance is that of the NHS and personal social services (see section 12.4.3 of the diagnostics assessment programme manual).
44	British Association of Stroke Physicians		- Both the XPECT data and the vast majority of data in the LINQ usability dataset come from people with known atrial fibrillation. Coupled with reports of high false positive alerts rates in observational studies using Reveal LINQ, there is some concern over the reported estimates of diagnostic accuracy in a cryptogenic stroke population.	Thank you for your comment which the committee considered. The committee noted that the base-case model did not include the cost of interpreting alerts produced by Reveal LINQ because of a lack of data on the number of alerts produced by the device. Including costs for reviewing alerts in the economic model would increase the base case ICER for Reveal LINQ. The EAG did 2 scenario analyses that included the costs of an optional triage service for alerts offered by Medtronic for Reveal LINQ. This increased the ICER by about £2,600 to £3,800 per QALY gained, depending on the cost option used. The clinical experts said that the costs used (£187 per patient per year or £374 per patient) are likely to be a realistic

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				estimate and could be considered a reasonable proxy for the costs of triaging alerts in the NHS (see section 4.12 of the diagnostic guidance document). Taking this, and other factors, into account, the committee concluded that while this would increase the base-case ICER, it was unlikely to increase to over £20,000 per QALY gained. The committee concluded that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained (see section 4.15 of the diagnostic guidance document).
45	Abbott Medical	4.5	"The committee concluded that there was good evidence that Reveal XT detected more people with atrial fibrillation than conventional follow up, and that this was likely to be seen in clinical practice." We suggest the consideration of sensitivity and specificity (i.e. false positive) be included since they are a key factor that determines the efficiency of care delivery.	Thank you for your comment which the committee considered. The committee considered that diagnostic yield was an appropriate measure to use to assess the cost effectiveness of implantable cardiac monitors over a long period of time, noting that this incorporates measures of device accuracy. The committee also noted that all positive results would be assessed by trained healthcare professionals before anticoagulants were offered reducing the chances of a false positive diagnosis. The committee noted that the base-case model did not

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				include the cost of interpreting alerts (including false positive alerts) produced by Reveal LINQ because of a lack of data on the number of alerts produced by the device. Including costs for reviewing alerts in the economic model would increase the base case ICER for Reveal LINQ. The EAG did 2 scenario analyses that included the costs of an optional triage service for alerts offered by Medtronic for Reveal LINQ. This increased the ICER by about £2,600 to £3,800 per QALY gained, depending on the cost option used. The clinical experts said that the costs used (£187 per patient per year or £374 per patient) are likely to be a realistic estimate and could be considered a reasonable proxy for the costs of triaging alerts in the NHS (see section 4.12 of the diagnostic guidance document). Taking this, and other factors, into account, the committee concluded that while this would increase the base-case ICER, it was unlikely to increase to over £20,000 per QALY gained. The committee concluded that the most plausible ICER for Reveal LINQ is likely to be less than £20,000 per QALY gained (see section 4.15 of the diagnostic guidance document).

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THEME: General comments and clarification

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46	Medtronic		Medtronic would like to thank NICE for the opportunity to comment on the Draft Guidance and support the recommendations made.	Thank you for your comment which the committee considered.
47	Medtronic		We apologise if information about the FocusOn monitoring service was not clear before, we kindly ask to remove "and within 1 hour" from the sentence to read: “The company says that red events are notified on the same working day from when the transmission reaches the CareLink Network service.”	Thank you for your comment which the committee considered. Section 2.18 of the diagnostics guidance document has been amended as suggested.
48	Medtronic		For accuracy, we suggest that “on” is replaced with “by” to read: “Amber events are notified via email by the next working day, and green events are aggregated and notified in a weekly email.”	Thank you for your comment which the committee considered. Section 2.18 of the diagnostics guidance document has been amended as suggested.
49	RCP		The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the BCS.	Thank you for your comment which the committee considered.